

13th International Symposium on HIV & Emerging Infectious Diseases



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June 3-5, 2004
Toulon, FRANCE

"Palais Neptune"
International Convention Center

Final Program & Abstracts Book

International Symposium on HIV & Emerging Infectious Diseases



<http://www.isheid.com>

International HIV Persistence Workshop



<http://www.hiv-workshop.com>

CME on HIV & AIDS



<http://www.hivaidsonline.com>

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Alain LAFEUILLADE, Toulon - FRA

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<http://www.isheid.com>

Scientific Secretariat / Secrétariat Scientifique

Doctor Alain LAFEUILLADE - Infectiology Unit, Chalucet Hospital - 83056 Toulon, France
Ph: + 33 (0)4 94 22 77 41 - Fax: + 33 (0)4 94 92 67 47 - E-mail: toulon2004@club-internet.fr

Logistic and Technical Organization / Organisation Logistique & Technique

OVERCOME - 3-5, bd Paul-Emile Victor, 92523 Neuilly-sur-Seine cedex, France
Ph: + 33 (0)1 41 92 01 20 - Fax: + 33 (0)1 46 41 05 21 - E-mail: hivcongress@overcome.fr

Chairman's Message

Dear Ladies, Gentlemen, Colleagues and Friends, I am delighted to welcome you to this 13th edition of the "International Symposium on HIV & Emerging Infectious Diseases". Your enthusiasm for this event, witnessed by over 900 registrations from every continent and an ever-increasing number of excellent quality abstracts, is truly encouraging and has made the last two years of preparation worthwhile. I would also like to thank the Steering and Scientific Committees for their availability and the work they have accomplished, as well as the many industrial partners who have made this meeting possible.

Although AIDS no longer motivates public authorities as it did at the epidemic's onset, it remains a major public health issue as far as we - the people who fight it on a daily basis - are concerned. It is continuing to spread in Africa and Asia, despite repeated alerts from the field and the front stage currently occupied by global health issues; this urgent situation is further exacerbated by the fact that vaccine research is making little headway. In addition, the current evolution of health care in our so-called developed countries is cause for concern, and forces us to conclude that economic management is gradually shunting the values of knowledge and solidarity. Fundamental research has also paid the price of this dangerous ethos, whose field of vision is limited to the very short term. Just one "unforeseeable" health crisis is enough to reveal our health systems are overwhelmed and no longer equipped to respond. Nevertheless, in our role as scientists and in honor of the many patients we have lost, our mission is to ensure the values of knowledge and humanism triumph over the barbarism of our decision-makers. In this sense, the AIDS story will have proved a certain degree of activism must imperatively be maintained, and will constitute our only effective weapon in the face of the emerging infectious diseases set to challenge tomorrow's world.

I wish you a pleasant stay in Toulon and a fruitful meeting!

Alain Lafeuillade



Message du Président

Mesdames, Messieurs, chers collègues et amis, C'est un grand plaisir pour moi de vous accueillir à cette 13^e édition du "Symposium International sur le VIH & les Maladies Infectieuses Emergentes". Votre participation nombreuse, avec plus de 900 inscrits représentant toutes les zones géographiques de la planète, le nombre croissant -ainsi que la qualité- des abstracts reçus, constituent le plus bel encouragement qui soit et justifient les 2 années de préparation qui viennent de s'écouler. Je remercie également le Comité d'Organisation et le Comité Scientifique pour leur disponibilité, pour le travail effectué, ainsi que les nombreux partenaires industriels qui permettent à ce congrès d'avoir lieu.

Même si l'infection à VIH ne motive plus les pouvoirs publics comme au début de l'épidémie, elle reste pour nous qui la combattons au quotidien un problème majeur de santé publique. Son évolution continue en Afrique et Asie, malgré les alertes répétées du terrain, la place au premier plan des préoccupations de sécurité sanitaire à l'échelle de la planète ; et l'urgence est d'autant plus grande que la recherche vaccinale piétine. L'évolution de nos systèmes de santé en pays dits développés est préoccupante. Force est de constater que la gestion économique a peu à peu pris le pas sur les valeurs de connaissance et solidarité. La recherche fondamentale a également fait les frais de ce système de pensée dont le champ de vision se situe à très court terme. Il suffit d'une crise sanitaire "imprévisible" pour constater que nos systèmes de soins sont dépassés et n'ont plus les moyens d'y répondre.

Notre mission pourtant, en tant que scientifiques et en mémoire des nombreux malades que nous avons perdus, est de faire triompher ces valeurs de connaissance et d'humanisme face à la barbarie de nos décideurs. L'histoire de l'infection à VIH a, dans ce sens, été une école qui prouve qu'un certain degré d'activisme doit toujours être maintenu. Il sera notre seul salut face aux maladies émergentes auxquelles nos sociétés seront demain confrontées...

Je vous souhaite un bon séjour à Toulon et un congrès fructueux !

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Thursday June 3, 2004 / Jeudi 3 Juin 2004

08.00 am Opening welcome desk / Ouverture de l'accueil

Vauban Amphitheater

09.30 am **Session: HIV, Virology / VIH, session virologique**
Chairs : Christine ROUZIOUX, Paris - FRA & Catherine TAMALET, Marseille - FRA

- **OP 1.1.** Recent Data on HIV Resistance to Antiretroviral Drugs
Données récentes sur la résistance aux antirétroviraux
Charles BOUCHER, Utrecht - NED
- How to Manage Cross-resistance ? / *Gestion des résistances croisées*
- **OP 1.2.** Resistance to RT Inhibitors / *Résistance aux inhibiteurs de la RT*
Anne-Geneviève MARCELIN, Paris - FRA
- **OP 1.3.** Resistance to PI / *Résistance aux IP*
Luc PERRIN, Geneva - SUI & Denis LACOSTE, Bordeaux - FRA
- **OP 1.4.** Resistance & Reservoirs / *Résistance & réservoirs*
Marie-Laure CHAIX, Paris - FRA
- **OP 1.5.** Rational Prescribing in the Era of HIV Phenotypic Drug Resistance Testing
Hess G, Nelson C, Lipskiy N. Surveillance Data, Plymouth Meeting PA, USA
- **OP 1.6.** Analysis of HIV-2 Resistance to Protease Inhibitors
Nogueira R., Coelho S., Freitas-Vieira A., Mammano F., Goncalves J.
URIA - Unidade de Retrovirologia e Doenças Infecciosas Associadas,
University of Lisbon, Faculty of Pharmacy, Lisbon - POR;
Laboratoire de Recherche Antivirale, INSERM U82, Paris - FRA
- **OP 1.7.** Polymorphism and Drug-selected Mutations in the Protease Gene of HIV-1
in Naive and Multi-treated Patient Isolates from the Seine-Saint-Denis District
in France: differences between B and non-B subtypes
Hawajri AL., Gault E., Aloui C., Drugan T., Le Gal F., Dziri-Mendil S., Dény P.
Laboratoire de bactériologie, virologie - hygiène, Hôpital Avicenne, AP-HP,
EA3406 ATHSCO, UFR SMBH, Université Paris 13, Bobigny - FRA;
University of Medicine and Pharmacy, Cluj - ROM

11.00 am Break, Posters, Exhibition / Pause, posters, exposition

Vauban Amphitheater

11.30 am **Workshop / Atelier**
Future Tendencies in Antiretroviral Therapy
Tendances future du traitement antirétroviral
President: Hervé GALLAIS, Marseille - FRA
Chairmen: François RAFFI, Nantes - FRA & Vincent CALVEZ, Paris - FRA

- **WS 1.1.** PI Cross-resistance / *Gestion des résistances croisées*
- The virologist's point of view / *le point de vue du virologue*
Bernard MASQUELIER, Bordeaux - FRA
- The clinician's point of view / *le point de vue du clinicien*
François RAFFI, Nantes - FRA
- **WS 1.2.** Tipranavir 2004 Update / *Tipranavir : Actualités en 2004*
Laurence WEISS, Paris - FRA
- **WS 1.3.** Tipranavir Compassionate Use and Expanded Access Program
Essai Compassionnel et Accès étendu du programme du tipranavir
Marie-Cécile CAMUS, Reims - FRA

Session in French only

Room Colbert



11.30 am **Meet the Experts Session / Session rencontre des experts**
Genotypic Tests and Drugs Pharmacokinetics in Patients with Treatment Failure: from theory to practice
Intérêt du génotypage et des dosages pharmacologiques dans la prise en charge des patients en échec de traitement : de la théorie à la pratique
 Chairman: Gilles PIALOUX, Paris - FRA

- **WS 2.1.** Contribution of Genotypic Tests / *Apport du Génotypage*
 Anne-Geneviève MARCELIN, Paris - FRA
- **WS 2.2.** Contribution of Pharmacokinetics / *Apport des dosages pharmacologiques*
 Gilles PEYTAVIN, Paris - FRA
- **WS 2.3.** Clinical Cases / *Cas cliniques*
 Patient with First Failure of Treatment / *Patient en premier échec de traitement*
 Patient with Failure of 3rd or 4th Line of Treatment / *Patient en échec de 3^e ou 4^e ligne de traitement*
 Gilles PIALOUX, Anne-Geneviève MARCELIN, Gilles PEYTAVIN, Paris - FRA

01.00 pm Break, Posters, Exhibition / *Pause, posters, exposition*

Vauban Amphitheater

02.00 pm **Session: HIV, Antiretroviral Strategies / VIH, stratégies antirétrovirales**
 Chairmen: Stefano VELLA, Roma - ITA & José GATELL, Barcelona - ESP

- **OP 2.1.** Initial Treatment Strategies / *Traitement de première ligne*
 Marianne HARRIS, Vancouver - CAN
- **OP 2.2.** New Antiretroviral Strategies / *Nouvelles stratégies antirétrovirales*
 Bernard HIRSCHHEL, Geneva - SUI
- **OP 2.3.** Managing Therapeutic Failure / *Gestion de l'échec thérapeutique*
 Bonaventura CLOTET, Barcelona - ESP
- **OP 2.4.** HIV Resistance & Therapeutic Strategies / *Résistance du VIH & stratégies thérapeutiques*
 Carlo Federico PERNO, Roma - ITA
- **OP 2.5.** Effects of Baseline Protease Inhibitor (PI) Mutations on the Efficacy of Ritonavir-Boosted Atazanavir (ATV/RTV) and Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Experienced Virologic Failure on Multiple HAART Regimens
 JOHNSON MA, London - UK

Vauban Amphitheater

03.00 pm **Symposium GILEAD Sciences**
Simplifying Antiretroviral Strategies: limits and benefits
Simplicité des stratégies antirétrovirales : limites et bénéfices
 Chairman: Alain LAFEUILLADE, Toulon - FRA



- **SS 1.1.** Triple NUC Combinations: real life clinical experience *versus* recently presented data
Trithérapies de NUC : confrontation d'une expérience clinique aux données récentes publiées
 Jean-Marie LANG, Strasbourg - FRA
- **SS 1.2.** Is Regimen Simplification Compatible with Effectiveness?
Impact de la simplicité sur la puissance des traitements antirétroviraux
 Bonaventura CLOTET, Barcelona - ESP
- **SS 1.3.** Update on Tenofovir Pharmacology
Dernières données de pharmacologie de Tenofovir
 Caroline SOLAS, Marseille - FRA



04.30 pm Break, Posters, Exhibition / *Pause, posters, exposition*

Vauban Amphitheater

05.00 pm **Session: HIV, Immunology / VIH, immunologie**
Chairmen: Giuseppe PANTALEO, Geneva - SUI & Jean-François DELFRAISSY, Paris - FRA

- **OP 3.1.** HAART-induced Immune Reconstitution: limitations & prospects
Reconstitution immune induite par la trithérapie : limitations & perspectives
Giuseppe PANTALEO, Geneva - SUI
- **OP 3.2.** New Insights into Immune Reconstitution / *Actualités dans la reconstitution immune*
Marie-Lise GOUGEON, Paris - FRA
- **OP 3.3.** State of the Art of anti-HIV Immunotherapy / *Etat des lieux de l'immunothérapie anti-VIH*
Giuseppe TAMBUSI, Milano - ITA
- **OP 3.4.** The Future of HIV Vaccine Development / *L'avenir de la recherche vaccinale*
Richard KOUP, Bethesda - USA
- **OP 3.5.** Humoral Immune Response Monitoring in HIV-1-infected Patients under anti-Tat Therapeutic Vaccine Trials
Zagury D., Le Buanec H., Badran BM., Willard-Gallo KE., Burny A. and Gallo RC.
Université P. et M. Curie; Néovacs, Paris; ULB, Bruxelles; Institute of Human Virology, Baltimore - USA

06.00 pm Welcome message / *Message de bienvenue*

Vauban Amphitheater

06.05 pm **Special Lecture / Conférence spéciale**
▪ **SL 1.1.** HIV Reservoirs: implications for therapy
Réservoirs du VIH : implications thérapeutiques
Roger POMERANTZ, Philadelphia - USA

06.30 pm Welcome cocktail in the exhibition / *Cocktail de bienvenue dans l'exposition*



Vauban Amphitheater

08.30 am **Session: HIV, Pharmacology & New Drugs**

VIH, session pharmacologique & nouvelles thérapeutiques

Chairmen: Gilles PEYTAVIN, Paris - FRA & Caroline SOLAS, Marseille - FRA

- **OP 4.1.** Optimal Use of Therapeutic Drug Monitoring in ARV Therapy
Utilisation optimale du suivi pharmacologique des antirétroviraux
David BURGER, Amsterdam - NED
- **OP 4.2.** The Search for New Antiretroviral Drugs / *Recherche de nouveaux antirétroviraux*
Erik DE CLERCQ, Leuven - BEL
- **OP 4.3.** New Antiretrovirals in the Gilead Pipeline / *Molécules développées par Gilead*
Jim ROONEY, Foster City - USA
- **OP 4.4.** TMC114: a new PI / *TMC114 : nouvel inhibiteur de protéase*
Eric LEFEBVRE, Yardley - USA
- **OP 4.5.** UK 427, 857: a promising new drug / *UK 427, 857 : nouvelle molécule prometteuse*
Chris HITCHCOCK, Sandwich - GBR
- **OP 4.6.** BMS 488043: a new HIV attachment inhibitor
BMS 488043 : nouvel inhibiteur d'attachement du VIH
Richard COLONNO, Wallingford - USA
- **OP 4.7.** PA 457: a novel anti-HIV drug candidate / *PA 457 : nouveau candidat anti-VIH*
Carl WILD, Gaithersburg - USA
- **OP 4.8.** SPD 754: a new RTI / *SPD 754 : nouveau RTI*
Richard BETHELL, Laval, Québec - CAN

10.30 am Break, Posters, Exhibition / *Pause, posters, exposition*

Vauban Amphitheater

11.00 am **Symposium Bristol-Myers Squibb**

A New Protease Inhibitor in Antiretroviral Strategies

Place d'un nouvel inhibiteur de protéase dans la stratégie de prise en charge

Chairmen: Alain LAFEUILLADE, Toulon - FRA & Françoise BRUN-VEZINET, Paris - FRA



- **SS 2.1.** Atazanavir Clinical Data / *Données cliniques d'un nouvel inhibiteur de protéase : Reyataz*
Roland LANDMAN, Paris - FRA
- **SS 2.2.** Atazanavir & Sensitivity Profile / *Reyataz & profil de sensibilité*
Richard COLONNO, Wallingford - USA
- **SS 2.3.** Pharmacokinetics Rationale for once-a-day Treatment
Prise unique quotidienne : pré-requis pharmacocinétiques
Thibaut LAVRUT, Nice - FRA
- **SS 2.4.** Which Factors to Consider for Managing Patients in 2004?
Facteurs déterminants dans la prise en charge thérapeutique des patients
Isabelle POIZOT-MARTIN, Marseille - FRA

12.30 pm Lunch, courtesy of Bristol-Myers Squibb / *Déjeuner offert par Bristol-Myers Squibb*

02.00 pm

Session: HIV, HAART Adverse Effects / VIH, effets secondaires de la trithérapie

Chairmen:

Pascale LECLERCQ, Grenoble - FRA & Alain LAFEUILLADE, Toulon - FRA

- **OP 5.1.** Management of Metabolic Complications of Antiretroviral Therapy
Gestion des complications métaboliques du traitement antirétroviral
Morrie SCHAMBELAN, San Francisco - USA
- **OP 5.2.** Update on HAART-induced Lipodystrophy
Actualités sur la lipodystrophie induite par les antirétroviraux
Jacqueline CAPEAU, Paris - FRA
- **OP 5.3.** In vitro Suppression of the Lipogenic Pathway by the non-nucleoside Reverse Transcriptase Inhibitor Efavirenz in 3T3 and Human Preadipocytes or Adipocytes
El Hadri K., Glorian M., Monsempe C., Dieudonné MN., Pecquery R., Giudicelli Y., Andreani M., Dugail I., Fève B. UMR CNRS 7079, Paris - FRA
- Panel Discussion / *Discussion avec les experts*
Pascale LECLERCQ, Grenoble - FRA, Alain LAFEUILLADE, Toulon - FRA,
Morrie SCHAMBELAN, San Francisco - USA, Jacqueline CAPEAU, Paris - FRA

03.00 pm

Symposium Roche

Place of Fusion Inhibitors in Therapeutic Strategies

Place des inhibiteurs de fusion dans les stratégies thérapeutiques

Chairman: Hervé GALLAIS, Marseille - FRA



- **SS 3.1.** Virological Data / *Données virologiques*
Jean-Claude TARDY, Lyon - FRA
- **SS 3.2.** 1st Clinical Case / *1^{er} Cas Clinique*
Alain LAFEUILLADE, Toulon - FRA
 - Discussion
Alain LAFEUILLADE, Toulon - FRA
Jean-Claude TARDY, Lyon - FRA
Rodolphe GARRAFFO, Nice - FRA
- **SS 3.3.** 2nd Clinical Case / *2^e Cas Clinique*
Laurent COTTE, Lyon - FRA
 - Discussion
Laurent COTTE, Lyon - FRA
Jean-Claude TARDY, Lyon - FRA
Rodolphe GARRAFFO, Nice - FRA
- **SS 3.4.** Guidelines / *Directives*
François RAFFI, Nantes - FRA
- Questions-Answers / *Questions-Réponses*

Best Poster Award by Roche Laboratory / Remise du prix poster par le Laboratoire Roche

04.30 pm

Break, Posters, Exhibition / *Pause, posters, exposition*

Vauban Amphitheater

05.00 pm **Special Lecture / Conférence spéciale**

- **SL 1.2.** New Concepts in anti-HIV Therapy / Nouveaux concepts du traitement anti-VIH
Robert GALLO, Baltimore - USA

Room Colbert

05.30 pm **Investigators Kaleobs Meeting / Réunion Investigateurs Kaleobs**

On invitation only / Sur invitation uniquement



Vauban Amphitheater

05.30 pm **Session: HIV in a Widened Europe / VIH dans une Europe élargie**

Chairmen: Yves MOUTON, Tourcoing - FRA & Emmanuel DELBEKE, Toulon - FRA

- **OP 6.1.** HIV in Central & Eastern Europe
VIH en Europe Centrale et Europe de l'Est
Caroline SEMAILLE, Paris - FRA
- **OP 6.2.** Family Systems for Substance Abuse & HIV Care in Ukraine
Systèmes de prise en charge en Ukraine
Natalia VLASOVA, Vinnitsa - UKR
- **OP 6.3.** HIV Infection in Estonia
Infection VIH en Estonie
Anneli UUSKULA, Tartu - EST
- **OP 6.4.** STDs in Slovakia
ISTs en Slovaquie
Emil TOMASIK, Bratislava - SLO
- **OP 6.5.** The Incidence of Viral Hepatitis Markers among Romanian Teenagers with Long-lasting Horizontally Acquired HIV Infection
Ruta S. Institute of Virology, Bucharest - ROM



“ **Saturday June 5, 2004 / Samedi 5 Juin 2004**

“ Vauban Amphitheater

08.15 am **Session: Viral Hepatitis / Hépatites virales**

Chairmen: Jean-Marie LANG, Strasbourg - FRA & Vicente SORIANO, Madrid - ESP

- **OP 7.1.** Treatment of HIV-HBV Coinfection
Traitement de la coinfection VIH-VHB
Yves BENHAMOU, Paris - FRA
- **OP 7.2.** Treatment of HIV-HCV Coinfection
Traitement de la coinfection VIH-VHC
Vicente SORIANO, Madrid - ESP
- **OP 7.3.** Tolerance of Viral Hepatitis Therapy in HIV-infected Patients
Tolérance du traitement des hépatites virales chez les patients infectés par VIH
Gilles PIALOUX, Paris - FRA
- **OP 7.4.** Role of the Hepatitis C virus-coinfection on Humoral Immune Alterations in HIV-infected Patients on HAART
Soriano-Sarabia N., Molina-Pinelo S., Delgado-Pecellin C., de Felipe B., Sanchez-Quijano A., Lissen, Leal EM., Vallejo A.
Group for the Study of Viral Hepatitis and AIDS,
Hospital Universitario Virgen del Rocio, Seville - SPA
- **OP 7.5.** Liver Transplantation in Five HIV-infected Patients With Virus Hepatitis Induced Cirrhosis
Radecke K., Frühauf NR., Miller M., Ross B., Köditz R., Malago M., Treichel U., Broelsch CE., Gerken G.
Department of Gastroenterology and Hepatology, Department of General Surgery and Transplantation, University Hospital Essen, Essen - GER

09.45 am Break, Posters, Exhibition / *Pause, posters, exposition*

“ Room Colbert

10.15 am **Session: Free oral Presentations, Basic Science / Communications libres**

Chairmen:

Jean-Pierre de JAUREGUIBERRY, Toulon - FRA & Catherine TMALET, Marseille - FRA

- **OP 8.1.** NF90ctv, a cellular dsRNA binding Protein Inhibits the Rev-dependent Export of HIV-1 RNA
Castaño ME; Kumar A and Urcuqui-Inchima S. Immunovirology Laboratory, Faculty of Medicine, University of Antioquia, Medellín - COL
- **OP 8.2.** Expression of HIV-1 gp160 in Transgenic Animals.
Berrada F., Al Akhawayn University in Ifrane. School of Science & Engineering, Ifrane - MAR
- **OP 8.3.** Polymorphisms in CCR5 promoter are associated with rare HIV-1 infection of the D32/D32 homozygous individuals
Xihau Lu, Ghalib Alkhatib, R. Tubiana and L. Meyer.
Indiana University School of Medicine, Indianapolis, Indiana - USA

- **OP 8.4.** Evaluation of Porcine Thymic Xenografts to Restore Human Thymopoiesis that is Resistant to HIV Infection
Hadidi S., Damrauer S., Lan P., Yang YG., Sykes M.
Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
- **OP 8.5.** Pol mutations and polymorphisms associated with NRTI and NNRTI-based regimens in Botswana patients infected with HIV-1 C.
Doualla-Bell F., Gaseitsiwe S., Ndung'u T., Modukanele M., Peter T., Novitsky V, Ndwapi N., Gaolathe T., Avalos A., Wester W., Bussmann H., Cardiello P., Marlink R., Moffat H., Thior I., Essex M., Wainberg MA.
McGill AIDS Centre- McGill University, Montreal, Canada; Botswana
Harvard Partnership for HIV Research and Education Gaborone, Botswana,
Harvard School of Public Health, Boston - USA
- **OP 8.6.** Aminoglycoside-arginine Conjugates: chemical barriers of HIV-1 entry
Lapidot A and Borkow G. Department of Organic Chemistry, Weizmann
Institute of Science, Rehovot - ISR
- **OP 8.7.** Pharmacological Blockade of Receptors Connecting To Inhibitory
Pathways Of Immune Cells May Be An Efficient Immunopotentiating Treatment
Of HIV/AIDS
Peuschel KE. Independent Researcher, Lugano - SUI
- **OP 8.8.** Structure of Viral Antitermination Complexes
Schwarz S., Scheckenhofer U., Prasch S., Eisenmann A., Schweimer K., Wöhl B., &
Rösch P. Lehrstuhl für Biopolymere, University, Bayreuth - GER
- **OP 8.9.** The VirtualPhenotype™ Analysis of an HIV-1 Genotype Provides a More Accurate
Prediction of Drug Susceptibility Than a Single Phenotype Measurement
Van Houtte M., Vermeiren H., Lecocq P., Winters B., Pattery T., Mc Kenna P., Bachelier L.
Virco BVBA, Mechelen, Belgium; VircoLab Inc, Durham, NC - USA

Vauban Amphitheater

10.15 am **Session: Free Oral Presentations Clinical Sciences / Communications libres**
Chairmen: Jean-Albert Gastaut, Marseille - FRA & Alain Lefeuvre, Toulon - FRA

- **OP 9.1.** Chinese SARS and AIDS Control at Frontier Ports
Mingchang S., Yonggui L., Yuping H. Madiandonglu Haidian District Beijing. P.R. - CHN
- **OP 9.2.** HIV-1 subtypes in the Northern Border Region of Kenya
Lihana RW, Lwembe RM, Kiptoo MK, Ochieng W, Oishi I, Ichimura H, Songok EM.
Kenya Medical Research Institute, Jomo Kenyatta University of Technology,
KEMRI/JICA Project, Nairobi - KEN
- **OP 9.3.** Method of Treatment of Acquired Immune Deficiency Syndrome with Embryonic
Hematopoietic Stem Cells
Smikodub OI. Cell Therapy Clinic of National Medical University and Embryonic Tissues
Center EmCell - UKR
- **OP 9.4.** Andrieu Unjustly Disregarded. Better CD4-counts with Prednisolone
Ulmer, Albrecht; Mueller, Markus; Frietsch, Bernhard. HIV-Practice, Stuttgart - GER

- 
- **OP 9.5.** Enhanced Immunogenicity of HIV-1 Whole Killed Vaccine in Association with Amplivax™
 Trabattoni D, Clivio A, Gori A, Bartholomew R, Fernandez-Cruz E, Lowry P, Kandimalla ER, Sullivan T, Bhagat L, Agrawal S, Clerici M, TheofanG, Bray DH. Dept Immunol, Dept Biol, Milano University, Dept Infect Dis, Milano, Italy; MRC Clinical Trials Unit, London, UK; Gregorio Maraon Univ Hospital, Madrid, Spain; Hybridon, Inc, Cambridge, Immune Response Co, Carlsbad - USA
 - **OP 9.6.** ESAT-6 and CFP-10 derived peptides for diagnosis of TB infection in severely immuno compromised HIV-infected individuals
 Fortis C, Tasca S, Mantegani P, Lazzarin A, Scarpellini P. IRCCS San Raffaele, Milano - ITA
 - **OP 9.7.** Why the Patient's Perspective is Critical in the Management of Lipodystrophy?
 Duracinsky M, Cervoni J, Bourgarit A, Sereni D, Molina JM, Wu A, Chassany O. Hopital de Bicêtre; Hopital Lariboisiere, Hopital Saint-Louis, Paris, France; Johns Hopkins University, Baltimore - USA
 - **OP 9.8.** A Technological Monitoring and Management-Support System for Anti-Retroviral Therapy in South Africa: Introducing Cell-Life
 S. Anand, U. Rivett, Cell-Life, University of Cape Town - South Africa

“Vauban Amphitheater

12.00 pm **Session: Update on SARS / Mise au point sur le SRAS**
 Chairmen: Alain LAFEUILLADE, Toulon - FRA & Gilles HITTINGER, Toulon - FRA

- **OP 10.1.** SARS: past, present, future / *SRAS : passé, présent, avenir*
 Tao HUNG, Beijing - CHN
- **OP 10.2.** Clinical Management of Patients with SARS / *Prise en charge des cas de SRAS*
 Joe SUNG, Hong Kong - CHN
- **OP 10.3.** The SARS-CoV S Glycoprotein, Mediator of Entry, Vaccine Immunogen and Target for Drugs / *La glycoprotéine CoV S du virus du SRAS, médiateur d'entrée, cible vaccinale et médicamenteuse*
 Dimiter DIMITROV, Frederick - USA
- **OP 10.4.** Detection & Quantification of the SARS-associated Coronavirus
Détection & quantification du coronavirus responsable du SRAS
 Leondios KOSTRIKIS, Nicosia - CYP
- **OP 10.5.** Concentration and Detection of SARS Coronavirus in Sewage from Xiao Tang Shan Hospital and the 309th Hospital of the Chinese PLA
 Li J, Wang XW, Chao FH, Li J, Zhen B, Kong Q, Son N, Jin M, Xiao W, Gu C, Yin J, Wei W. Institute of Hygiene and Environmental Medicine, Academy of Military Medical Sciences, P.R. China; Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences, Beijing, P.R - CHI
- **OP 10.6.** Purification, Characterization, and Immunogenicity of a Truncated Form of the SARS Spike Protein: Toward a recombinant glycoprotein subunit vaccine
 Kan E, Coates S, Stadler K, Matsuoka K, Calderon E, Song H, Seo MY, Winger M, Barnett S, Ulmer J, Rappuoli R, Abrignani S, Houghto, M, Han J, Srivasta I. Chiron Corporation, Emeryville, USA; IRIS, Chiron S.r.l., Siena - ITA

01.00 pm Break, Posters, Exhibition / *Pause, posters, exposition*

02.15 pm **Session: Concerns in HIV Care / Inquiétudes dans la prise en charge du VIH**

Chairmen: Alain LAFEUILLADE, Toulon - FRA & Alain RIEU, Toulon - FRA

- **OP 11.1.** AIDS in Africa: a terrible injustice
Le SIDA en Afrique : une terrible injustice
Marie-José MBUZENAKAMWE, Bujumbura - BDI
- **OP 11.2.** Has HIV Prevention some Efficacy in the Developed World?
La prévention du VIH est-elle efficace dans les pays développés ?
Didier LESTRADE, Paris - FRA
- **OP 11.3.** HIV no longer a Disease Apart?
Le VIH perd-il le statut de maladie particulière ?
Gilles PIALOUX, Paris - FRA
- **OP 11.4.** Economic Threats on Fundamental Research
Menaces économiques sur la recherche fondamentale
Jean-Louis VIRELIZIER, Paris - FRA
- Panel & Participants Discussion / *Discussion entre les orateurs & les participants*

03.30 pm **Session: Poster Discussion / Discussion de Posters**

Several posters in each track will be selected by the Scientific Committee and discussed with the participants & authors / *Plusieurs posters dans chaque thème seront sélectionnés par le Comité Scientifique et discutés avec les participants et leurs auteurs*

04.30 pm Closing / *Clôture*



HIV, Epidemiology

- **PP 1.1** Trends in the HIV/Aids Epidemic in Women in the City of São Paulo, 1985 - 2000
Tancredi MV, Waldman EA. Referral and Training Centers for STD/Aids - São Paulo, Sao Paulo - Brazil
- **PP 1.2** Les Jeunes Parlent aux Jeunes.
Diatta A, Ndiaye MA, FALL MF. Groupe Communication Internationale en Technologie Cultures et Services en Afrique (G.CITCS Afrique), Dakar - Senegal
- **PP 1.3** Serological Profiles in Hemodialysed Patients of Constantine
Semra Z, Ait Kaki B, Boulkhadra A.
Laboratoire de Microbiologie CHU Constantine - Algeria
- **PP 1.4** Sero-epidemiological aspects of the HIV infection in Algeria
Ait Kaki B, Belabbes E, Bouguremouh A. Laboratoire de Microbiologie CHU Benbadis, Constantine & Institut Pasteur Virologie, Alger - Algeria
- **PP 1.5** Surveillance of HIV/AIDS. Epidemiological Trends. Cuba: 1986-2003
Torres Peña R, Joanes Fiol JJ, Lantero Abreu MI, Estévez G.
Ministry of Public Health, National Aids Program, Havana City - Cuba
- **PP 1.6** The Vertical Transmission of the Pediatric AIDS in Cuba
González I, Díaz M, Pérez J. Instituto Pedro Kouri Ciudad Habana - Cuba
- **PP 1.7** Correlation of HIV Prevalence Rates Between Sexually Transmitted Diseases Patients And Pregnant Women Attending Antenatal Clinic In India
Kant S, Shaukat M. All India Institute of Medical Science, National AIDS Control Organisation, New Delhi - India
- **PP 1.8** The Rate of HIV/AIDS from 1987 to 2003 in Belarus and Influence of Injecting Drug Users on the Expansion of HIV Infection
Kaskevich IA. Vitebsk State Medical University - Belarus
- **PP 1.9** HIV Infection: present persisting problems for pregnant women and their babies and families
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 1.10** Temporal Trend of Fatality Events in a Cohort of 1,214 Heroin Drug Addicts Followed Since 1977 in Bologna, Italy. Role and evolution of HIV-associated deaths
Manfredi R, Sabbatani S, Agostini D, Chiodo F. Infectious Diseases, University of Bologna, and Department of Public Health, Bologna - Italy
- **PP 1.11** Introduction to Risk Mapping and Behavioural Analysis as Tools to Fight against STI/HIV/AIDS: the case of Douala Cameroon
Jeanne d'Arc KENGNE. Association Culturelle Mission de Recréation (ACMR), Douala - Akwa Douala - Cameroon
- **PP 1.12** Pluses of HIV/AIDS Peer education Training For Adolescents In Uganda.; A Case of the AIDS Challenge Youth Club
Sentamu SPS, Lukwago BL. The AIDS Support Organisation, Kampala - Uganda

- **PP 1.13** Health Seeking Behaviour-Means of Stimulating Youth Into Seeking It?
Sentamu SPS.The AIDS Support Organisation, Kampala - Uganda
- **PP 1.14** The Professional Insertion of AIDS-infected Young Girls
Muyuku EM, Munyana MM.Swaa-Burundi, Bujumbura - Burundi
- **PP 1.15** The Role of Religious Doctrines in Prevention of AIDS
Esmaeelzadeh M, Ghanbari M. Mashhad University of Medical Sciences, Mashhad - Iran
- **PP 1.16** The Role of IV Drug Users`s Control in Prevention of AIDS
Ghanbari M, Esmaeelzadeh M. Mashhad University of Medical Sciences, Mashhad - Iran
- **PP 1.17** Screening of Iranian Blood Donors for Transfusion Transmitted Infections
Moniri R., Mossavi G.A. Kashan University of Medical Sciences - Iran
- **PP 1.18** Prostituées de Rue et VIH : interactions sexuelles et logiques de gestion du risque.
Trottier G, Damant D, Paré G, Doitteau N, Noël L, et Michel Dorais
Laval University, School of Social Work, Québec - Canada
- **PP 1.19** Sexual Behaviour of Female Undergraduates in the Freshman Year at the University of
Ibadan, Nigeria
Faseru B, Sangowawa AO, Okoro CA, Lawoyin TO.
University College Hospital, Ibadan - Nigeria
- **PP 1.20** Epidemiological Features of Tuberculosis in Northern Italy, and Public Health Care
Correlates
Manfredi R, Sabbatani S, Legnani G, Chiodo F
Infectious Diseases, University of Bologna - Italy
- **PP 1.21** International Charity Organization "Rehabilitation Center "STEPS", Vinnitsa branch,
Ukraine, Activities.
Vlasova N.
Vinnitsa Branch of International Charity Organization "Steps", Vinnitsa - Ukraine
- **PP 1.22** Evolving Assistance Features at an Infectious Disease Day-Hospital Service, in Relation
with the Natural History of HIV Infection in the Highly Active Antiretroviral Therapy
(HAART) Era
Manfredi R, Calza L, Chiodo F
Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 1.23** To Foster Awareness Against AIDS
Sarker AH. Physiotherapy Center, Dhaka, Bangladesh
- **PP 1.24** Immigration and HIV Infection in Northern Italy. Inpatient Admissions, 2000-2003
Manfredi R, Calza L, Chiodo F
Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 1.25** Disasters on Medications and Technical Behaviour Condition
RoseJoshi. Kathmandu - Nepal
- **PP 1.26** Stigma Attached to HIV / AIDS : Implications for Health Care and Social Adjustment in
Mumbai
Chauhan SL. National Institute for Research in Reproductive Health, Mumbai - India
- **PP 1.27** The Problems and Effects of Mother to Child (MTC) HIV Transmission in an Extended
Family System in Ghana. Duodu MO, Osei-Ntim O, Agyekum D, Afriyie KO, Amponsah G.
Beware of AIDS (BAWA), Manchester - UK

- **PP 1.28** The Economic and Educational Problems of HIV/AIDS' Infection in Rural Ghana
Duodu MO, Mohammed MY, Osei-Ntim O, Adusei K, Amponsah G. Beware of AIDS (BAWA), Manchester - UK
- **PP 1.29** Premarital Sex Towards Infertility and STD'S Infection
Smith C. Kwadaso-Kumasi - Ghana
- **PP 1.30** A Bridge of HIV Transmission Between Injection Drug Users and General Population in Ukraine
Kyrychenko PD, Vlasova N. Vinnitsa Pirogov National Medical University, International Charity Organization "STEPS", Vinnitsa branch, Vinnitsa - Ukraine
- **PP 1.31** Trends in HIV Risk Behaviors in Castellon, Spain
Roca B, Ventura JM, Tornador N, Bahamonde D. Hospital General of Castellon - Spain
- **PP 1.32** Multi Drug Resistant Tuberculosis (MDR-TB) And Public Health Policy
Atre SR. The Foundation for Research in Community Health, Pune - India
- **PP 1.33** Reducing and preventing HIV/AIDS and other STIs incidence and prevalence among cross-cultural groups in South Florida, Haiti and Jamaica: A Tri National Project.
Delva F, Fanfan MF. Florida International University, Florida Memorial College, Miami, University of South Florida, Tampa, Florida - USA
- **PP 1.34** Factors Associated with Continuation of High-risk Behaviour by HIV-positive Injection Drug Users
Kyrychenko P. Vinnitsa Pirogov National Medical University, Vinnitsa - Ukraine
- **PP 1.35** Lost Opportunities of Detection of HIV Infection during Pregnancy in Brazil
Szwarcwald CL. Fundação Oswaldo Cruz, Rio de Janeiro - Brazil
- **PP 1.36** Prise en Charge des Enfants Orphelins du SIDA
Jacquie Militoni. Santé et Développement Communautaire, RDC
- **PP 1.37** Infant Feeding in the Context Of HIV/AIDS: a Call to Action
Liles C, Tompson M. AnotherLook, Evanston, Illinois - USA
- **PP 1.38** Surveillance study of selected sexually and blood transmitted infections in HIV-negative vs. HIV-positive pregnant women and their newborns in SR.
Stanekova D, Adamcakova J, Kopilcova T, Kotuliak J, Vaculikova E, Habekova M, Mokras M. Slovak Health University, Bratislava - Slovakia
- **PP 1.39** Mobilisation des Femmes Infectées et Affectées par le VIH/SIDA pour une Large Réponse à l'Epidémie
Outiama P. Dpt Santé, PVVS, Bangui, RCA
- **PP 1.40** Public health surveillance of sexual exposure to HIV in the French Armed Forces in 2002
Michel R, Ollivier L, Aiesi F, Meynard JB, Boutin JP. IMTSSA, Marseille - France
- **PP 1.41** Guaranteed Education on Safe Sex and HIV Related Infections for Cameroonians in Relation to Blood Donation: Itoe F, Natural Initiative for Voluntary Blood Donors - Cameroon
- **PP 1.42** Prevalence of HCV Specific antibody, RNA and genotypes among HIV infected Iraqi haemophiliacs : Al-Kubaisi WA, Al-Nahrain University/Medical College, Baghdad - Iraq
- **PP 1.43** HIV/AIDS, STI Prevention And Sex Education In Nepalese Schools/Colleges Youths : Gautam R, Koirala M. BP Memorial Health Foundation, New Baneshwor - Kathmandu, Nepal

- **PP 1.44** The women's antenatal care initiative for reduction of HIV mother-to-child transmission in Colombia - The Mother & Child Project - (project funded by the European Commission) : García Bernal R, Arenas Granada CD, Prieto Alvarado FP, Rincón Ramirez JA, Vargas LE, Ramirez Ramirez CM. UNAIDS, Bogotá - Colombia
- **PP 1.45** Prevalence of Drug-Resistant HIV Mutants In Recently Infected And Naïve Patients In Liguria, A North-Western Region of Italy: Setti M, Bruzzzone B, Ventura A, Murdaca G, Frabetti M, Icardi G, Indiveri F. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa - Italy
- **PP 1.46** Occupational Exposure to HIV, HBV and HCV Among S. Martino Hospital Health Care Workers (Genoa) in the Years 1989 To 2003: Setti M, Cardinale F, Riccio C, Sticchi C, Talassio G, Frabetti M, Icardi G, Bruzzzone B. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa - Italy
- **PP 1.47** Ethics in the Information: Silva HMS. University of Itaúna, Itaúna, Faculty of Formiga, Formiga , Faculty of Pará de Minas, Pará de Minas - Brazil
- **PP 1.48** Knowledge, Perception And Acceptability Of Microbicides (KPA) Among Non-health Care Givers In Lagos, Nigeria: Smith SI, Agomo C, Idigbe EO
Nigerian Institute of Medical Research, Lagos - Nigeria
- **PP 1.49** Lubricants Containing N-9 May Enhance Rectal Transmission of HIV and Other STIs: Phillips D, Sudol K, Taylor C, Guichard L, Elsen R, Maguire R
Population Council, New York & Sexual Health project, San Francisco - USA
- **PP 1.50** HIV/AIDS As a Part of Health Policy - Acceptance
Lakhani A, Saiyyad YA. Deepak Charitable Trust, Vadodara - India
- **PP 1.51** HIV/AIDS & Women's Economic Empowerment
Lakhani A. Deepak Charitable Trust, Vadodara - India
- **PP 1.52** HIV/AIDS Care And Support Program
Annappoorani TM, Roberts VA, MacDonald LC. BLOSSOM, Virudhunagar - India
- **PP 1.53** Coinfection of Hepatitis B and Hepatitis C Virus among HIV Patients in Ho Chi Minh City Vietnam
Vo TTN, Nguyen HC, Maynard M, Nguyen VN, Ngo TKC, Pham VH, Truong XL, Follezou JY. Tropical Medicine Hospital, Pasteur Institute in Ho Chi Minh city, Binh Trieu Hospital, Preventive Medicine Center, Ho Chi Minh, Vietnam; University of Paris VI, Paris - France
- **PP 1.54** Mentality of PLWH/A and Affected Families in the Slum-based Poorest of Poor Community
Swamy G, Bansode S. John Paul Slum Development Project, Pune - Indonesia
- **PP 1.55** Demographics of HIV Patients Referred for Initial Visits to a NYC Clinic
Jin S. Suh, Kinga Chieloszyk, Robert Warford, Phyllis Ristau, Victoria Sharp, New York - USA
- **PP 1.56** Homosexuality and HIV/AIDS in Kathmandu, Nepal:
Pkhakadze G. University of Madras, Department of Anthropology, Chennai - Nepal

HIV, HCV, Basic Science

- **PP 2.1** The Core Protein of Hepatitis C Virus is a Potent RNA Chaperone Promoting Dimerization of the Viral Positive-Strand RNA
Ivanyi-Nagy R, Cristofari G, Gabus C, Boulant S, Lavergne JP, Penin F, Darlix JL
LaboRetro, INSERM U412, ENS de Lyon, IBCP CNRS, Lyon - France
- **PP 2.2** The Design of HIV-1 Infection Laboratory Model in Cotton Rats
Rytik PG, Kutcherov II, Muller WEG, Poleshchuk NN
Research Institute, Minsk - Belarus
- **PP 2.3** A Newly Developed Provirus Quantification Assay using Real-time SYBR Green I PCR and its Validation in a Murine AIDS Model
Casabianca A, Orlandi C, Fraternale A and Magnani M. Institute of Biological Chemistry "Giorgio Fornaini", University of Urbino, Urbino (PU) - Italy
- **PP 2.4** Different Mechanisms of HIV-1 RT-mediated Homologous and Non-homologous Recombination
Kurzynska-Kokorniak A, Jankowska A, Jackowiak P, Alejska M, Figlerowicz M
Institute of Bioorganic Chemistry Polish Academy of Sciences, Noskowskiego, Poznan - Poland
- **PP 2.5** Influence of Antigenic Peptide Structure and Delivery System on the Level and Polarization of Immune Response
Maksyutova AV, Bulychew LE, Maksyutov AZ, Poryvaev VD, Lebedev LR, Ryzhikov AB.
SRC VB "Vector", Koltsovo, Novosibirsk - Russia
- **PP 2.6** Identify the Cellular Factors that Interact with Retrovirus Receptors using Yeast-Two Hybrid System
Rezvan M, Tailor CS, Kashan University of Medical Sciences - Iran
- **PP 2.7** HIV-1 5'UTR Functions as a Ryboswitch Regulating Genomic RNA Replication and Recombination
Urbanowicz A, Jankowska A, Berkhout B, Figlerowicz M. Institute of Bioorganic Chemistry Polish Academy of Sciences, Noskowskiego, Poznan - Poland
- **PP 2.8** A Novel CCR5 Mutation Selectively Affects Immunoreactivity and Fusogenic Property of the HIV Co-receptor in a Slow Progressing HIV Patient
Zhao XY, Lee SS, Wong KH, Chi-Wai Chan K, He ZM, Ma S, Chung-Sing Chan C, Mun-Hon Ng, Zheng BJ
HIV Research Laboratories, Department of Microbiology, the University of Hong Kong; Integrated Treatment Centre, Department of Health; Hong-Kong - China
- **PP 2.9** The P40 ORF1 Product of The Human LINE-1 Retrotransposon Possesses Sequence Similarities To HIV-1 Gag
Zhou JL, Kim SJ, Kirou KA, Crow MK. Hospital for Special Surgery, New York - USA
- **PP 2.10** Automation of Sample Preparation for Quantitative HIV RNA PCR LCx assay
Muller Z, Stelzl E, Kessler HH.
Department of Clinical Microbiology, Szekesfehervar, Hungary, Molecular Diagnostic Laboratory, Institute of Hygiene, KF-University, Graz - Austria
- **PP 2.11** Intracellular Concentration of Indinavir (IDV) in Patients with AIDS Receiving Two Different Dosages of Indinavir/ritonavir (IDV/rtv)
Garraffo R, Lavrut T, Simonet P and Pugliese P
Nice University Hospital and Cannes General Hospital - France

- **PP 2.12** Effect of HIV Protease Inhibitors on P-glycoprotein Expression in Peripheral Blood Mononuclear Cells: an in vivo and in vitro study.
 Le Saint C, Charnay Y, Lafeuillade A, Vincent JP and Cupo A
 Institut de Pharmacologie Cellulaire et Moléculaire UMR-CNRS 6097, Valbonne, France; Hôpitaux Universitaires de Genève, Division de Neuropsychiatrie, Genève, Suisse; Unité Infectiologie, Hôpital Chalucet, rue Chalucet, Toulon - France
- **PP 2.13** The intracellular content of phosphorylated metabolites of AZT and d4T may be quantified in HIV infected patients by two independant specific immunoassays .
 Le Saint C, Menguy V, Lafeuillade A, Vincent JP and Cupo A. Institut de Pharmacologie Cellulaire et Moléculaire UMR-CNRS 6097, Valbonne; Unité Infectiologie, Hôpital Chalucet, rue Chalucet, Toulon - France
- **PP 2.14** Low Impact of MDR1 Genotype on the Pharmacokinetic (PK) Parameters of Indinavir (IDV) in HIV-Infected Patients Treated or Not with Low-dose Ritonavir (RTV)
 Solas C, Poizot-Martin I, Simon N, Bourgarel-Rey V, Dinh T, Sampol-Manos E, Villard PH, Gastaut JA, Lacarelle B. Timone Hospital, Sainte-Marguerite Hospital, UMR-CNRS 6032, University of Mediterranee, Marseille - France
- **PP 2.15** CD4 and CD14 Receptors Down-modulation by Potent Microbicide Lithium-Iodophore
 Davtyan TK, Hakobyan IS, Gabrielyan ES
 CJSC "Armenicum" Clinical Centre, Yerevan - Armenia
- **PP 2.16** HIV-1 decoy TAR and vif siRNA Expressed as a Single RNA Molecule under the Human U6 Promoter Enhanced the Inhibition Efficacy of HIV-1 Replication in Transduced Cells.
 Barnor JS, Miyano-Kurosaki N, Abumi Y, Shiina H, Ishikawa K, Yamamoto N, Osei-Kwasi M, Ofori-Adjei D, and Takaku H. Department of Life and Environmental Science and High Technology Research Center, Chiba Institute of Technology, Chiba-Japan; National Institute of infectious Diseases, AIDS Research Center, Tokyo-Japan; Noguchi Memorial Institute for Medical Research, Department of Virology, Accra-Ghana, and Tokyo Medical and Dental University, Tokyo - Japan
- **PP 2.17** Novel Dimerization Inhibitors acting at the Nanomolar Level : a class of antiproteases to overcome drug resistance in HIV-1 chemotherapy
 Collinet B, Bannwarth L, Boggetto N, Dumond J, Ongerli S, Merabet N, Van Baelinghem L, Sicsic S, Reboud-Ravaux M. Laboratoire d'Enzymologie Moléculaire et Fonctionnelle, Institut Jacques Monod, UMR 7592, CNRS-Universités Paris 6 & 7, Paris, France; Laboratoire de Reconnaissance Moléculaire et Synthèse, Biocis, UMR-CNRS C8076, Faculté de Pharmacie, Université de Paris-Sud, Châtenay-Malabry - France
- **PP 2.18** Sulfonic Acid Polymers as Extracellular HIV-1 Tat and gp120 Proteins Antagonists
 Bugatti A, Urbinati C, Goffi F, Camozzi M, Liekens S, De Clercq E, Presta M, Rusnati M. General Pathology and Immunology, Department of Biomedical Sciences and Biotechnology, University of Brescia, Italy. & Rega Institute for Medical Research, Leuven - Belgium
- **PP 2.19** Mutations Conferring Drug-resistance of the Reverse Transcriptase of Human Immunodeficiency Virus Subtype G.
 Garaev MM, Pazilin AS, Shemshura AB, Saukhat SR.
 Institute of Virology, Moscow - Russia
- **PP 2.20** Effects of Antiretroviral Exposure and Genotypic Mutations in Predicting Phenotypic Resistance to Atazanavir (ATV), Lopinavir (LPV), and Tenofovir (TDF) in Patients Naïve to these Drugs.
 Samson P, Rutstein R, Schnittman S, Ortiz A, Graham B, Fenton T, Aldrovandi G, and the Pediatric AIDS Clinical Trials Group P1020A Study Team. Boston, USA

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- **PP 2.21** Microbicidal and Virucidal Action of Antioxidants and their Interaction with Iodophores
Hovhannisya HGn. CJSC "Armenicum" Clinical Centre, Yerevan - Armenia
 - **PP 2.22** Full Transcriptome Analysis of Genes Altered by HIV in Macrophages
Ottonnes F, Lejeune M, Manchon L, Piquemal D, Commes T, Marti J. Institut de Génétique Humaine, CNRS UPR 1142, Skuld-Tech, Université Montpellier II, Montpellier - France
 - **PP 2.23** Enhanced Degradation of Drug-resistant HIV-1 Reverse Transcriptase is Mediated through Proteasomal Pathway
Starodubova ES, Pazlin AS, Karpov VL, Isaguliants MG. Institute of Molecular Biology, Institute of Virology, Moscow, Russia; Institute of Infectious Diseases, Stockholm - Sweden
 - **PP 2.24** Parameter Identification of an HIV/AIDS Dynamical Model
Ouattara DA, Bugnon F, Moog C, Raffi F. IRCCyN (Institut de Recherche en Communication et Cybernétique de Nantes), UMR CNRS 6597, & CHU de Nantes, Centre d'Information et de Soins de l'Immunodéficience humaine, Nantes - France
 - **PP 2.25** The Carboxyl-Terminus of HIV-1 Integrase Facilitates Viral Nuclear Import
Cunningham C, Topper M, Muesing MA. Rockefeller University, Aaron Diamond AIDS Research Center, New York - USA
 - **PP 2.26** Molecular Homology Between Alpha-defensin And Scrub Typhus Rickettsia Orientia Tsutsugamushi 56kd Type Specific Antigen
Tran MKG, Kirkiacharian S, Maurisson G, Caprani A. University, Paris Sud XI, Faculty Pharmacy, Chatenay Malabry, Centre Medical Europe, University Paris Jussieu, Paris - France
 - **PP 2.27** HIV-1 Protease is a Metalloproteinase Containing a Copper-Binding Motif Gly his Lys (GHK) at Residues 68-70
Tran MKG, Kirkiacharian S, Maurisson G, Caprani A, University, Paris Sud XI, Faculty Pharmacy, Chatenay Malabry, Centre Medical Europe, University Paris Jussieu, Paris - France
 - **PP 2.28** Incorporation of nucleoside analogs into mitochondrial DNA decreases in the presence of p53 protein.: Bakhanashvili M, Novitsky E, Levy I, Rahav G. Unit of infectious Diseases, Sheba Medical Center, Tel-Hashomer - Israel
 - **PP 2.29** High Levels of HIV-1 Infection of CD8 Lymphocytes Expressing CD4 in vivo: Cochrane A, Leen C, Scott G, Simmonds P, University of Edinburgh, Edinburgh - UK
 - **PP 2.30** Evaluation of the Abbott LCx HCV-RNA Quantitative Assay: Ceccherini-Nelli L, Malizia T, Giannotti A, Vanni M, Lico S, Avena S, Moriconi F, Comastri G, Pulvirenti FR, Thamm S, Campa M. Dipartimento di Patologia Sperimentale B.M.I.E., U.O. di Microbiologia Universitaria, AOUP, Pisa, Abbott Molecular Diagnostics, Roma, Italy; Abbott Molecular Diagnostics, Wiesbaden - Germany
 - **PP 2.31** Comparison Among Three Different Systems of Genotype Interpretation in HIV Resistance Testing: Setti M, Ventura A, Bruzzzone B, Nigro N, Demetri A, Caligiuri P, Cardinale F, Lai P, Department of Internal Medicine, Department of Health Sciences, university of Genoa, Genoa - Italy
 - **PP 2.32** Partial Resistance To HIV- 1 Disease Progression Induced By SDF 1 3'UTR A 801 G Polymorphism: A Molecular Explanation: Rueda P, García-Moruja C, Torres MC, Alcamí J, Caruz C. Dpto. Biol. Exp. Universidad de Jaén, Jaén, C.N.B.F. Instituto de Salud Carlos III, Madrid - Spain

- **PP 2.33** Carraguard* Prevents Macrophage Trafficking from Vagina: implications for microbicide development: Perotti ME, Pirovano A, Phillips D. University of Milan, Italy; Population Council, New York - USA
- **PP 2.34** Human Immunodeficiency Virus Transactivator Protein (Tat) Induces a Calcium Increase Through L-type calcium channels of Human Monocytes
Contreras X, Bennasser Y, Chazal N, Moreau M, Leclerc C, Bahraoui E.
Laboratoire d'immuno-virologie, Centre Biologie Développement,
Université Paul SABATIER, Toulouse - France
- **PP 2.35** HIV-1 Tat Directly Binds To NF B Enhancer Sequence: Role In Viral And Cellular Gene Expression
Dandekar DH, Mitra D, Ganesh KN. Organic Chemistry Synthesis, National Chemical Laboratory, National Centre for Cell Science, Pune - India
- **PP 2.36** Molecular Mechanism of Methionine-enkephalin on the Suppression of SIV infected Lymphocyte Apoptosis
Li P, Liu X, Li G, Xu J. Department of biochemistry and molecular biology,
Peking University, Beijing - China
- **PP 2.37** A Rationally Designed CD4 Miniprotein, Useful to Discover Specific Ligands of HIV-1 GP120 Glycoprotein
Stricher F, Martin L, Mechulam A, Mons S, Barthe P, Roumestand C, Ménez A, Veas F, Vita C. Département d'Ingénierie et d'Etudes des Protéines, CEA Saclay, Gif-sur-Yvette, Laboratoire d'Immunologie Rétrovirale et Moléculaire, IRD/CNRS, Centre de Biochimie Structurale, Université de Montpellier, Montpellier - France
- **PP 2.38** Morphine stimulate apoptosis of SIV infected CEM x174 cells
Xu J , Li PF, Liu XH, Li G. Department of biochemistry and molecular biology, Peking University, Heath Science Center, Beijing 100083 - China
- **PP 2.39** Different Characteristics of HCV-specific CD8+ T Cell Responses in Chronic HCV Infection, HIV Coinfection and Spontaneous Clearance
Barrett L, Howley C, Hirsch G, Peltekian K, Bowmer MI, Grant M.
Memorial University of Newfoundland, St. John's, St. John's Health Care Corporation, Dalhousie University, Halifax - Canada

HIV, Clinical Science

- **PP 3.1** The Value of PCR HIV RNA for Early Detection of HIV Infection
Pescic I, Zerjav S. CCS-Institute for Infectious and Tropical Diseases - Virology Department, Belgrade - Serbia & Montenegro
- **PP 3.2** Management of HIV/TB coinfection in Cuba
Díaz Jidy M, González Nuñez I, Pérez Avila J. Institute Pedro Kouri Autopista Novia del Medio Dia, La Haban, Habana - Cuba
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Goyal HK, Singla M, Gupta RP. Government Medical College, Patiala - India
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Onayemi O, Oninla O. A. Department of Dermatology & Venereology, Faculty of Clinical Sciences, Obafemi Awolowo University, Ile-Ife - Nigeria
- **PP 3.5** Acute HCV in a Cohort of HIV-positive Men - Outcomes And Response To Pegylated Interferon-alpha 2b and Ribavirin
Bhagani S, Danta M, Fernandez T, Slapak G, Dusheiko G, Johnson MA.
Royal Free Hospital London - UK

- **PP 3.6** Gynecomastia in an Adolescent with Perinatal HIV Infection: associated variables
Manfredi R, Calza L, Chiod Fo. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
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Plaisance N, Lang JM, Beck-Wirth G, Chartier C, Hansmann Y, Michel C, Audhuy B. Hôpitaux Civils de Colmar; Hôpitaux Universitaires de Strasbourg; CH de Mulhouse - France
- **PP 3.8** Acquired Immunodeficiency Syndrome (AIDS) and Multiple Neoplastic Malignancies as Emerging Conditions in the Era of Highly Active Antiretroviral Therapy (HAART)
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 3.9** Cardiac Tumor in an HIV-1 Patient
Comenda E, Cardoso O, Goncalves P, Machado J, Maltez F, Mourao L. Hospital de Curry Cabral, Lisboa - Portugal
- **PP 3.10** Vasculitic Neuropathy in HIV Infection
Minijagap P, Jahathesan K. M.G.R Medical University, Chennai - India
- **PP 3.11** Cognitive Impairment in HIV Patients under HAART : neurophysiological and neurometabolic evaluation
Poizot-Martin I, Blanquet F, Frixon-Marin V, Michotey P, Drogoul MP, Gastaut JA, Planche D, Vion-Dury J. Service de Neurophysiologie, Hôpital de la Conception, CISIH, Hôpital Ste Marguerite, IRM, Hôpital Ambroise Paré, Service de Neurophysiologie, Hopital de la Timone, et Institut des Neusociences Cognitives de la Méditerranée (INCM, UMR CNRS 6193, Marseille - France
- **PP 3.12** The Epidemiology of the Cryptococcosis within the Sick VIH (Hospital point G) in 2002
Alassane OumarA.A.O , Dao S, Doumbo OK, Diallo M, Diallo A, Poudiougou. PB.Faculté Medecine, Pharmacie, Bamako - Mali
- **PP 3.13** Multiple Subcutaneous Lipomas during HIV Disease: which relationship with antiretroviral therapy and dysmetabolism?
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 3.14** Metabolic and Renal Profile before and after Tenofovir DF
Roca B, Gisbert C, Cabestany B, Perez AP, Ventura JM. Hospital General of Castellon - Spain
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Pitche P, Drobacheff-Thiebaut C, Gavignet B, Mercier M, Laurent R. Department of Dermatology, CHU Saint-Jacques, Besançon - France
- **PP 3.16** HIV-HCV Coinfection. Hospital de Navarra (1995-2003)
Sola J, Gatesi C, Layana E, Castiello J, Reparaz J, Sola I. Servicio Enfermedades Infecciosas, Pamplona - Spain
- **PP 3.17** Study of HIV-infected patients attending an Intensive Care Unit (ICU). Features and prognostic. Comparative analysis between pre- and post HAART eras
Palacios R, Reina C, Santos J, de la Torre MV, Márquez M. Hosp. Virgen de la Victoria. Campus Teatinus, Málaga - Spain

- **PP 3.18** Fulminating Lactic Acidosis in a Woman with Disseminated Tuberculosis and Advanced HIV in the Absence of anti-retroviral Therapy
Marshall BG, Rowen D, Addis B. Southampton University Hospitals NHS Trust
Tremona Road, Southampton, SO16 6YD, Hampshire - UK
- **PP 3.19** Increasing AIDS "Presenters: a further concern of the Highly Active Antiretroviral Therapy (HAART) Era
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
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Göhde W, Cassens U, Greve B. Institute of Radiobiology, Institute of Transfusion Medicine, University Hospital, Münster - Germany
- **PP 3.21** HIV-Associated Psychiatric Disorders
Farazi E. Mashad University of Medicine - Iran
- **PP 3.22** Management of hyperlactatemia in three HIV-positive patients assuming ART
Moretti F, Quiros-Roldan E, Prestini K, Torti C, Casari S, Carosi G. Department of Infectious and Tropical Diseases, University of Brescia, Brescia - Italy
- **PP 3.23** Malabsorption and Septicaemia: Association in and Implications for Children in an Area of High HIV Prevalence : Chhagan MK, Kauchali S. University of KwaZulu-Natal, Nelson R Mandela School of Medicine, Durban - South Africa
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Dua S, Wajed S, Winslet M.
University Dept of Surgery, Royal Free Hospital, Pond Street, London NW3
- **PP 3.25** ARVs Side Effects Leads To Poor Compliance Hence Resistance
Byaruhanga BR, Mugenyi MP, Kityo KC, Otim OT, Mwebesa MD. Joint Clinical Research Center, Kampala - Uganda

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- **PP 4.2** Impact of the Adverse Effects of HAART in Various Clinical Situations on the 3/5 Initiative of WHO-resource Limited Country Setting: a pilot study
Ketha P. State Nodal Officer for the Control of AIDS, Project Implementation Plan, Phase II, National AIDS Control Organisation, Andhra Pradesh -India
- **PP 4.3** Care and Treatment Issues of PLWHAs in Resource Poor Conditions
Agrawal R & Ghosh P. Bhoruka Public Welfare Trust, Kolkata - India
- **PP 4.4** Scaling up Antiretroviral Therapy in Jamaican Children
Evans-Gilbert T, Pierre R, Steele -Duncan J, Rodriguez B, Whorms S, Figueroa, PJ, Christie CDC. Bustamante Hospital for Children Kingston - Jamaica
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Vivona V, Vincentelli J, Drogoul MP, Marimoutou C, Poizot Martin I, Penot Ragon C, Gastaut JA.
Pharmacie Hôpital, CISIH-SUD Unité d'Hématologie-VIH Hôpital Sainte Marguerite, Marseille - France

- **PP 4.6** Prise en Charge Communautaire des PVVIH Soins de Santé de Base à Domicile par les Jeunes Volontaires en Lutte contre le SIDA (AJVLS) : visite à domicile dans Lomé-Commune (TOGO)
Association des Jeunes Volontaires en Lutte contre le SIDA (AJVLS), Lomé - Togo
- **PP 4.7** Close Collaboration between Physician and Virologist for a Stage CDC-3 AIDS Patient : importance of genotype assessment for the choice of efficient antiretroviral therapy
Duloust A, Naudin CA, Cottreau D, Jauneau M. Centre Médical de Bligny, Briis/forges - France
- **PP 4.8** High Prevalence of Nephrolithiasis in HIV- infected Patients Co-infected with Hepatitis C Virus Treated with Indinavir+Ritonavir
Dragovic G, Jevtovic Dj. Institute of Clinical Pharmacology; Pharmacology and Toxicology, School of Medicine, University of Belgrade, Belgrade; Institute of Infective and Tropical Disease - HIV/AIDS Unit - School of Medicine, University of Belgrade, Belgrade - Serbia & Montenegro
- **PP 4.9** The Phenomenon of HIV-infected Patients taking only Isolated Dual Nucleoside Analogue Antiretroviral Therapy, Eight Years after HAART Introduction.
Practical issues and concerns
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 4.10** Impact of the HCV Co-infection in Naïve HIV-1 Infected Patients Treated with HAART
Silva S, Ferreira A, Tavares M, Piñeiro C, Xerinda S, Serrão R, Diaz-Brito V, Marques R, Mota Miranda A. Infectious Diseases Department, Hospital S. Joao & School of Medicine, Porto - Portugal
- **PP 4.11** Nelfinavir in HCV - HIV coinfecting patients: 24 Months' follow up
Poizot-Martin I, Marimoutou C, Drogoul-Vey MP, Vion-Dury F, Frixon-Marin V, Benhaim S, Poggi P, Gastaut JA. CISH-SUD- Hematology- HIV Unit, Clinical Research Department Sainte-Marguerite Hospital, CHU of Marseilles - France
- **PP 4.12** Predictive Factors for Saquinavir-ritonavir combination (SQV/r) Efficacy in Real Life
Tissot-Dupont H, Mars-Kallee ME, Montestruc F, Tomei C, Martin S, Lecomte V, Gallais H. La Conception Hospital, Marseille, France; Roche Laboratories, Neuilly - France
- **PP 4.13** Saquinavir-ritonavir Baby Dose Combination (SQV/r) : Same efficacy and better tolerance in real life than Saquinavir-Ritonavir high dose (SQV/R)
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- **PP 4.14** Influence du Passage à l'Association Lamivudine, Zidovudine, Abacavir (TRIZIVIR) sur l'Observance des Traitements Antirétroviraux.
Jouglen J, Clement F, Minot A, Lacoste D, Pometan JP. Service Pharmacie, Service de médecine interne, CHU de Bordeaux, Hôpital Saint-André, Bordeaux - France
- **PP 4.15** Relevance of Lopinavir/r Therapy in Heavily pre-treated Patients
Sola J, Layana E, Alaez JI, Sola I, Uriz J, Castiello J, Reparaz J. Clinico Universitario, Madrid - Spain
- **PP 4.16** Metabolic Evaluation of Kaletra (LPV/r)-containing Regimens
Lafeuillade A, Hittinger G, Geoffroy M, Poggi C, Delbeke E, Jolly P, Lambry V, Philip G. General Hospital, Toulon - France

- **PP 4.17** Antiretroviral Usage in a Large Metropolitan Area of Northern Italy. Selected drugs and related costs
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 4.18** A Comparison of the Two First-line Recommended Antiretroviral Regimens for Naïve HIV-infected Subjects
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
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Akomiah P, Bio T, University of Cape Coast, Cape Coast - Ghana
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Monpoux F., Tricoire J., Lalande M, Reliquet V, Thuret I. CHU de Nice, Toulouse, Montpellier, Nantes, Marseille - France
- **PP 4.21** Efficacy Evaluation of Combined Chemoprophylaxis of Vertical HIV Transmission
Shostakovich-Koretskaya LR, Hozhilo II, Chykarenko ZA, Cherginets AV.
Dniepropetrovsk State Medical Academy, Dniepropetrovsk - Ukraine
- **PP 4.22** A Pilot Study Evaluating the Efficacy and Safety of a Bioadhesive Buccal Tablet of Miconazole 50 mg (Miconazole Lauriad™) in HIV Positive Patients with Oropharyngeal Candidiasis
Dupont B, Dellamonica P, Datry A, Consigny PH, Kirstetter M, Poizot-Martin I, Meyohas MC, Chaumont C, Croughs T, Lafeuillade A. Hosp Necker, Hosp Pitié Salpêtrière, Hosp Bichat, Private institution, Hosp Saint Antoine, BioAlliance Pharma, Paris; Hosp Archet, Nice; Hosp Sainte Marguerite, Marseille; Hosp Chalucet, Toulon - France
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Murenzi FC, Van Den Ende J. National University Of Rwanda, Kigali - Rwanda
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Carbonnel E, Claudy A. Hopital E. Herriot, Lyon - France
- **PP 4.25** Use of Pyrimethamine-Sulfadoxin in Treatment of Cerebral Toxoplasmosis in HIV Infected Patients
Gomez JE, Alvarado F, Hernandez C, Cuervo S, Saravia J. Centro Investigaciones bio medicas, Universidad del Quindio - Colombia
- **PP 4.26** Therapeutic Drug Monitoring (TDM) of Nelfinavir (NFV): Recommendations for Optimization
Laurent S, Sigrist H, Solas C, Poizot-Martin I, Chadapaud S, Frixon-Marin V, Lafeuillade A, Dhiver C, Moreau J, Pichancourt G, Ravaux I, Cohen Valensi R, Ruer J, Lacarelle B. Timone Hospital, Sainte-Marguerite Hospital, Conception Hospital, Nord Hospital, Marseille; Chalucet Hospital, Toulon; Henri Duffaut Hospital, Avignon; Martigues Hospital, Martigues - France
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Boivin H, Nau P, Andre V, Rouleau A. Pharmacy CHRU Tours, - Hospital Bretonneau - France
- **PP 4.28** Comparison of Efficacy of Two Interventions to Enhance Adherence to Antiretroviral Therapy (HAART)
J. Benkimoun J, Gnamien S, Dupont C, Chaltiel L, Aubry N, Le Mercier F, Rouveix E, Lebas-Certain M. Department of Pharmacy & Department of Internal Medicine, Hôpital Ambroise Paré (AP-HP), Boulogne - France

- **PP 4.29** Cultural Adaptation and Validation of a Lipodystrophy Quality of Life Questionnaire
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- **PP 4.30** Persistent Low Viremia and Future Treatment Options
Dyner T, Cafaro V, Chow V. Shared Perspectives on Therapies, San Francisco - USA
- **PP 4.31** Impact of Highly Active Antiretroviral Therapy (HAART) on Blood Pressure (BP) in Patients with HIV Infection. A prospective study in a cohort of naïve patients
Palacios R, Santos J, Castell E, González M, Ruiz J, Márquez M. Hosp Virgen de la Victoria. Campus Teatinus, Málaga - Spain
- **PP 4.32** HIV Positive Patients' Perspectives about their Adherence to Antiretroviral Therapy
Morillo García A., Gasch Illescas A., Valencia Martín R., Aldana Espinal JM, Conde Herrera M. Virgen del Rocío Hospital, 41013 Sevilla - Spain
- **PP 4.33** Patients-reported Factors Influencing Adherence to Antiretroviral Therapy
Montana M, Darque A, Ravaux I, Gallais H, Gensollen S, Bongrand MC, Timon-David P. Hospital Pharmacy, Infectious Diseases Wards, Conception Hospital, Marseille - France
- **PP 4.34** Antiretroviral Prescriptions Proved Significant Different Between the Two Outpatient Centres of a Metropolitan Area in Northern Italy: An Analysis of Economic Correlates
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 4.35** Comparison of Toxicity and the Dyslipidemic profile of the Two Available non-nucleoside Reverse Transcriptase Inhibitors: significant differences between Nevirapine and Efavirenz
Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna - Italy
- **PP 4.36** Glycyrrhizin Production from Transformed Licorice Cells
Kovalenko P.G., Maliuta S.S. Institut of Molecular biology and genetics NASU, Zabolotnogo, Kiev -Ukraine
- **PP 4.37** Efficacy of Enfuvirtide in Patients Infected with a Drug-resistant Human Immunodeficiency Virus (HIV-1)
Lebaudy C, Ghnassia C, Poinssignon Y. Vannes Hospital - France
- **PP 4.38** Natural Treatment for HIV/AIDS
Schelonka EP. Good News Medical Clinic, Belize City, Belize - Central America
- **PP 4.39** Vivre avec le Secret du VIH et des Multithérapies pour un Groupe de Femmes Montréalaises
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- **PP 4.40** Two-drug ART in Treatment Naïve HIV-infected Persons in Resource-limited Setting: 2-year study
Yanamadala VMKR. Association of People Against AIDS, Kakinada, Andhra Pradesh - India
- **PP 4.41** The Dissociation Between Immunologic and Virologic Response to HAART
Pesic I, Salemovic D, Ranin J, Zerjav S, Jevtovic Dj. The Institute of Infectious and Tropical Diseases, Belgrade - Serbia & Montenegro
- **PP 4.42** Utilization of HIV Post Exposure Prophylaxis Among Health Care Workers in Selected Health Institutions In Nairobi
Maina JW, Wasunna MK, Orago AS, Okelo RO. Kenyatta University, Nairobi - Kenya

- **PP 4.43** High Thymic Volume and Output at Baseline is Associated to Enhancement of Viral Replication and Immunologic Impairment Early after HAART Discontinuation in Chronic HIV Infection
Vallejo A, Valladares A, De Felipe F, Vivancos J, Soriano-Sarabia N, Gutierrez S, Molina-Pinelo S, Ruiz-Mateos E, Lissen E, Leal M. Hospital Virgen del Rocío, Seville - Spain
- **PP 4.44** The Benefit of the Combination Antiretroviral Therapy (ART) for the Treatment of HIV Infected Patients in Slovakia
Habekova M, Stanekova D, Mokrá M. Slovak Health University - Institute of Preventive and Clinical Medicine, Department of Geographical and Infectious Medicine of Derer Hospital, Bratislava - Slovakia
- **PP 4.45** Virologic Efficacy and Pharmacokinetic of Saquinavir/Ritonavir Baby Dose once Daily (QD) combination in PI (protease inhibitor) Pretreated HIV-1 + Patients: Brunel-Dalmas F, Livrozet JM, Gagnieu MC, Bru JP, Michon C, Touraine JL. Hôpital E. Herriot, Lyon, Hôpital d' Annecy, Roche, Neuilly-sur-Seine - France
- **PP 4.46** Early HCV-RNA Kinetic In HIV Patients With Chronic Hepatitis C Treated With PEG-IFN Alpha-2a And Ribavirin: Setti M, Bianchi S, Basso M, Sticchi C, Pelli N, Murdaca G, Indiveri F, Picciotto A. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa - Italy
- **PP 4.47** Nanoparticles Associated to Zidovudine as an Innovative Approach for Targeting Intestinal Reservoir During HIV Infection: Dembri A, Soursac M, Thomas CM, Maquin A, Cheret A, Ponchel PG, Constantini D. Bioalliance pharma, Paris, Laboratoire de Pharmacie Galénique, Université Paris XI, Châtenay-Malabry - France
- **PP 4.48** Higher Risk of Antimalarial Treatment Failure in HIV Positive than in HIV Negative Individuals with Clinical Malaria: Van Geertruyden JP, Mwananyanda L, Chalwe V, Mwanakasale V, Moerman F, Chilengi R, Kestens L, D'Alessandro U. Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium; Tropical Diseases Research Centre, Ndola - Zambia
- **PP 4.49** Inhibitor Design for Drug-Resistant Forms of Aspartic Protease of HIV: Frecer V, Miertus S. International Centre for Science and High Technology, UNIDO, AREA Science Park, Trieste - Italy
- **PP 4.50** Efficacy of Enfuvirtide (FUZEON®) in HIV1-Infected Patients with Failure or Intolerance to Antiretroviral Treatment: Faye F, Darque A, Ravaux I, Gallais H, Gensollen S, Timon-David P, Bongrand MC. Pharmacy, Public Hospital System Conception, Infectious diseases ward, Marseille - France
- **PP 4.51** PC-815, a Novel Combination Microbicide: Romero JF, Thorn M, Phillips D. Population Council, New York - USA
- **PP 4.52** Lack of an Effect of Atazanavir on Steady-State Pharmacokinetics of Methadone in Chronically Treated Subjects
Friedland G, Andrews L, Agarwala S, Schreiber T, Daley L, Child M, Wang Y, O'Mara E. Yale School of Medicine, New Haven, CT; Bristol-Myers Squibb, Princeton, NJ, USA
- **PP 4.53** Follow Up of the Resistance Mutations Archives During Genotype Guided HAART
Parisi SG, Mazzi R, Gatti F, Carolo G, Nicastrì E, Concia E, Dal Bello F, Montano M, Palù G, Andreoni M. Microbiology Dept, Padua Hospital, Padua, Public Health Dept, Tor Vergata University, Rome, Infectious Diseases Dept, Verona Hospital Verona - Italy
- **PP 4.54** Long Term Immunological Benefit with Double Nucleoside Therapy : Genotype Markers
Parisi SG, Mazzi R, Sarmati L, Gatti F, Carolo G, Concia E, Montano M, Dal Bello F, Palù G, Andreoni M. Microbiology Dept, Padua Hospital, Padua, Public Health Dept, Tor Vergata University, Rome, Infectious Diseases Dept, Verona Hospital Verona - Italy

- **PP 4.55** HIV-1 Drug Resistance Among Tunisian Subjects With Therapeutic Failure
Jlizi A, Ben Halima M, Slim A, Tebourski F, El Gaaied A, Ben Chaabane T, Chakroun M, Letaief-Ommezin A, Garbouj M. Laboratoire de Microbiologie, Hôpital Charles Nicolle, Laboratoire de Génétique Moléculaire, Immunologie et Biotechnologie, Faculté des Sciences, Service de Pathologie Infectieuse, Hôpital La Rabta, DSSB, Ministère de la Santé Publique, Tunis, Service de Pathologie Infectieuse, Hôpital Fattouma Bourguiba, Monastir, Service de Pathologie Infectieuse, Hôpital Farhat Hached, Sousse - Tunisia
- **PP 4.56** Relative Quantification of Human Immunodeficiency Virus type 1 proviral DNA in Patients undergoing Structured Treatment Interruption
Kabamba-Mukadi B, Henrivaux P, Ruelle J, Bodeus M and Goubau P.
Université Catholique de Louvain, Bruxelles, Service de Médecine interne, Clinique Saint Joseph, Liège - Belgium.
- **PP 4.57** Safety Assessment of Patients Receiving Atazanavir (ATV) With Ritonavir (RTV), ATV With Saquinavir (SQV), or Lopinavir (LPV)/RTV: 48-Week Results From BMS AI424-045: Clotet B, Lazzarin A, Grinsztejn B, Lichtenstein K, Sankoh S and Wilber R. IrsiCaixa Foundation, Barcelona, Spain; S. Raffaele Hospital, Milan, Italy; Instituto de Pesquisa Clínica Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil; University of Colorado Health Sciences, Denver, CO; Bristol-Myers Squibb, Wallingford, CT, USA

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Sriwanthana B, Jitjuk B, Wichukchinda N, Rojanawiwat A, Tanaka M, Pathipvanich P, Ariyoshi K, Sawanpanyalert P. National Institute of Health, Nonthaburi, Lampang Hospital, Lampang, Thailand
- **PP 5.2** Effects of Exogenous Nef Protein on Immune System
Pugliese A, Petrini S, Beltramo T, De Checchi S, Gallo G & Vidotto V. Department of Medical and Surgical Sciences, Section of Clinical Microbiology of Turin University, "Amedeo di Savoia" Hospital, Turin - Italy
- **PP 5.3** Construction of Candidate DNA-Vaccines against HIV
Babkina IN, Pozdnyakov SG, Ryazankin IA, Babkin IV, Shchelkunov S. State Research Center of Virology and Biotechnology "Vector", Koltsovo, Novosibirsk region - Russia
- **PP 5.4** Poly-CTL Epitope Immunogen, Candidate for DNA-vaccine against HIV-1
Bazhan SI, Belavin PA, Seregin SV, Danilyuk NK, Babkina IK, Karpenko LI, Nekrasova NA, Lebedev LR, Ignatyev GM, Agafonov AP, Ilyichev AA. SRC VB Vector; Koltsovo, Novosibirsk Region - Russia
- **PP 5.5** Mimotopes of Human Immunodeficiency Virus Type 1 Diagnostic and Neutralizing Envelope Epitopes
Gazarian K, Palacios Y, Gazarian T, Mailuf A. Mexican Nacional Autonomous University, Mexico City, Mexico; Regional Hospital Gabriel Mancera, Mexico City - Mexico
- **PP 5.6** Different Delivery Systems for Artificial Polyepitope HIV-1 Antigen: Nekrasova N A, Ignatyev G M, Agafonov AP, Lebedev LR, Ilyichev A A, Karpenko LI. The State Research Center of Virology and Biotechnology "VECTOR" Koltsovo, Novosibirsk Region - Russia
- **PP 5.7** Effects of Poly-glycine Linker on the Presentation of the Foreign Epitopes : Shahrokhi N, Bouzari S, Jafari A. Pasteur Institute of Iran, Tehran - Iran
- **PP 5.8** Chimeric Core Particles HBcAg Carrying Epitopes from Pres Region of HBV Surface Protein
Veremeiko TA, Lebedev LR, Zaitsev BN, Nekrasova NA, Ilyichev AA, Karpenko LI
The State Research Center of Virology and Biotechnology "VECTOR" Koltsovo, Novosibirsk Region - Russia

- **PP 6.1** Helinx Technology Inactivates High Titers of SARS-CoV, WNV and Vaccinia in Platelet Concentrates
Dupuis K, Sampson-Johannes A, Bernard K, Sawyer L. Cerus Corporation, Concord, CA; New York State Dept. of Health, Slingerland, NY - USA
- **PP 6.2** Chinese Herbal Medicine for Severe Acute Respiratory Syndrome (SARS): a Systematic Review and Meta-Analysis
Liu JP, Manheimer E, Shi Y, Gluud C. Liverpool School of Tropical Medicine Liverpool, UK ; University of Maryland School of Medicine, Baltimore, USA; Shanghai University of Traditional Chinese Medicine, Shanghai, China; Copenhagen University, Copenhagen - Denmark
- **PP 6.3** Mucosal Immunogenicity of Surface-displayed SARS Viral Antigens on Lactic Acid Bacteria
Kim CJ, Lee JS, Poo H, Sung MH. College of Veterinary Medicine, Chungnam National University, Bioleaders Corp., Korea Research Institute of Bioscience and Biotechnology, Daejeon, Korea - South
- **PP 6.4** The Role of TT Virus (TTV) Infection in Human Pathology - The Analysis of Observed Cases
Tomasiewicz K, Modrzewska R, Krawczuk G, Łyczak A. Department of Infectious Diseases Medical University of Lublin - Poland
- **PP 6.5** Out of Africa: A Sorry Safari
Uslan DZ, MD and Sia IG. Mayo Clinic, Rochester MN - USA
- **PP 6.6** Association of a Novel Perforin Gene Polymorphism with HTLV-I Infection in Mashhad, North East of Iran
Farid R, Kharazmi A, Nobahar V. Mashhad University of Medical Sciences, Mashhad - Iran
- **PP 6.7** Clinical Profile of Dengue Outbreak in Delhi
Bhoi S, Kheira A, Wasir J. All India Institute of Medical Sciences, New Delhi - India
- **PP 6.8** Comparison of HCV RNA and HCV Core Antigen Kinetics in the Follow-up of a Therapeutic Protocol in HCV-HIV Coinfected Patients (RIBAVIC)
Lunel F, Pivert A, Payan C, Morand P, and the members of the Ribavir Scientific Committee (ANRS HC02). Laboratoire de Bactériologie-Virologie, CHU Angers, France ; Laboratoire de Virologie, CHU Grenoble - France
- **PP 6.9** Prophylactic and Therapeutic Effects of Small Interfering RNA Targeting SARS-Coronavirus
Zheng Bj, Guan Y, Tang Q, Cheng D, Xie FY, He ML, Chan KW, Wong KL, Lader E, Woodie MC, Lu PY, Li B, Zhong N. Department of Microbiology, Institute of Molecular Biology, Department of Pathology, University of Hong Kong, Hong Kong - China
- **PP 6.10** An Exceptional Case Report of Very Early Tertiary Syphilis in a Young Adult
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OP 1.1.
Recent Data on HIV Resistance to Antiretroviral Drugs

No abstract available

OP 1.2. Resistance to RT Inhibitors

Dr Anne-Geneviève Marcelin
Service de Virologie - Hôpital Pitié-Salpêtrière
83 bd de l'hôpital - 75013 Paris
anne-genevieve.marcelin@psl.ap-hop-paris.fr

Considerable progress has been made in defining the indications for resistance testing and determining the cost-effectiveness of strategies that use testing in the management of HIV-infected individuals. Prospective randomized trials have shown at least short-term virological benefits for both genotypic and phenotypic resistance testing in a variety of situations. Moreover, emerging data indicate that viral drug resistance is a problem wherever treatment is used, and it may be increasing in importance. It has also become clear that knowledge concerning patterns of resistance and cross-resistance is critical to the development of successful sequencing of antiretroviral regimens.

The specific mechanisms of nucleoside reverse transcriptase inhibitor (NRTI) resistance are now better understood, as well as the observed levels of resistance associated with the various patterns of mutations encountered in clinical practice.

Two distinct resistance pathways toward NRTI emerged. Some reverse transcriptase mutations lead to an enhanced excision of the analogue from the nascent DNA strand; other mutations reduce the incorporation efficiency of the nucleotide triphosphate form of the NRTI.

The removal of the chain-terminator after it has been incorporated into the growing chain can occur in one of two mechanisms. In one mechanism, the pyrophosphate reacts in the presence of mutations to facilitate removal of the chain terminator and take it out of the growing chain. This opens up a site for substrate to come in and carry on growth, and the virus escapes inhibition. The second mechanism involves a process when NTP acts as a donor to remove the chain terminator. Instead of pyrophosphate being released when the nucleoside analogue triphosphate is incorporated into the viral DNA chain, the presence of multiple resistance mutations in reverse transcriptase prevents translocation and allows removal of the nucleoside analogue. The extension process can then proceed by the addition of a cellular nucleoside building block.

This mechanism of resistance within reverse transcriptase concerns the mutations selected by zidovudine (41L, 67N, 70R, 210W, 215Y/F, and 219E/Q) that tend to accumulate during continued exposure to zidovudine in the absence of good viral suppression. Recently, it has been appreciated that these mutations can also be selected by stavudine, and that they have implications for resistance to all drugs in the NRTI class and to the recently FDA-approved nucleotide reverse transcriptase inhibitor, tenofovir. Thus, these mutations are probably best referred to as nucleoside analogue mutations (NAMs), since they can affect the entire class.

The other NRTI resistance pathway that occurs through the efficiency of discrimination concerns mainly single point mutations, like M184V, K65R and L74V.

The 184V mutation that can result in up to 1000-fold increases in resistance to lamivudine also appears to interact with NAMs to modulate resistance to all the other NRTIs. In reverse transcriptase that contains no more than 2 or 3 NAMs, this mutation enhances translocation during reverse transcription, decreasing excision of the nucleoside analogue residue. However, as the number of NAMs increases, 184V does not have enough effect to prevent excision.

The take-home message is that NAMs are bad for this class of antiretrovirals, and the accumulation of high numbers of these mutations should be assiduously avoided. Thus, viral load and resistance monitoring should be used together to ensure that therapy is changed before high numbers of NAMs evolve. The appearance of the 184V mutation may improve sensitivity to many of the drugs in this class, but it will not "reverse" high-level resistance. Nonetheless, inclusion of lamivudine in salvage regimens may improve the effectiveness of the NRTI components of therapy, and it is certainly a well-tolerated drug -- an important issue for most patients receiving salvage therapy.

In conclusion, the critical problem in the clinical setting is that a mutant selected for by a failing regimen may have some degree of cross-resistance to other drugs in the same class that have not yet been prescribed to that patient. The development of cross-resistance may lead to a reduced virologic or immunologic response to subsequent regimens. As scientists develop new agents active against resistant virus, clinical medicine is also implementing diagnostic strategies designed to detect antiretroviral resistance and individualize subsequent regimens.

OP 1.3.

Gestion des Résistances croisées (RC) aux Inhibiteurs de Protéase (IP), le point de vue du clinicien

Denis Lacoste, Bordeaux - France

Ce n'est pas heureusement encore le problème des résistances primaires peu fréquentes sauf cas particuliers, mais c'est un des challenges d'aujourd'hui que de ne pas compromettre l'avenir thérapeutique des patients en ciblant les premières lignes thérapeutiques de façon à ne pas risquer de voir apparaître de mutations barrant la route aux IP en seconde intention.

S'informer et se former est ici plus que jamais devenu indispensable, ainsi que maintenir son niveau de connaissance.

Les échanges entre cliniciens, virologues, pharmacologues sont désormais la clé de la qualité de prise en charge des patients nécessitant un traitement anti-rétroviral (ARV).

La communauté scientifique est de plus en plus convaincue de la nécessaire prise en compte de l'archivage des mutations dans l'histoire thérapeutique des patients, déterminant les choix d'associations d'ARV.

Les recommandations nationales sont de bons guides à priori mais l'analyse au cas par cas reste la plus part du temps souhaitable.

Prévenir les RC fait partie du quotidien

- Soit en première intention, par l'épargne des IP, ou si un schéma avec IP est recommandé, faire le bon choix adapté au contexte.
- Soit en seconde intention ou en nième ligne de traitement, savoir corriger les choix avec l'aide d'algorithmes à jour, se faire aider des avis spécialisés comme cela est dit plus haut; des choix comme l'utilisation d'autres classes d'ARV, l'interruption thérapeutique seront discutés.

Des IP " Stars " apparaissent en terme de mutagénèse et/ou de simplification thérapeutique... Doit-on toujours céder aux sirènes ?

Enfin, que dire des possibilités restreintes de certains pays où l'avenir est en train de se jouer au fil des mises à disposition parfois anarchiques de tel ou tel IP ?

OP 1.4. Resistance & Reservoirs

No abstract available

OP 1.5.

Rational Prescribing in the Era of HIV Phenotypic Drug Resistance Testing

G. Hess, C. Nelson, N. Lipskiy

Surveillance Data, Plymouth Meeting PA USA

Objective: In the U.S. patients newly diagnosed with HIV infection are generally treated initially with three-drug regimens. Although guidelines have emerged encouraging the use of resistance testing to help guide therapy, access and insurance coverage for the service varies across the US. In addition, while average resistance on a national level may be known, there may be regional differences. Clinicians prescribing decisions may also be influenced by considerations beyond reduced susceptibility i.e. resistance. We studied and compared phenotypic resistance and antiviral prescribing trends by different regions in the U.S during July 2002 to June 2003, the HAART era.

Methods: An automated sample of patient-level phenotypic resistance testing data from Virologic Inc. was retrospectively analyzed for July 2002-June 2003. Test results were mapped to their respective zip codes. Antiviral retail prescription data covering approximately 65% of the U.S. population was analyzed for the same period and geographies. Phenotypic resistance by class and antiviral prescribing by class (NNRTI, NRTI and PI) was compared for each of the four U.S. census regions. Results were analyzed using regression and descriptive statistics for significant differences.

Results: There were approximately 22,000 patient specimens tested against all marketed HIV antivirals for a total of 330,000+ drug resistance tests in the study period. Approximately 1.5 million HIV antiviral retail scripts were dispensed and analyzed for the same period. 1) HIV resistance and antiviral prescribing was inversely correlated for NNRTIs i.e. resistance was highest for NNRTIs and its share of prescriptions was the lowest. 2) Although NRTI resistance was higher than PI resistance, NRTI prescribing was still significantly higher than PI prescribing across all regions. 3) HIV phenotypic resistance was statistically different by region for each class of drugs with the exception that there was no difference in resistance in the South compared to the West for NNRTIs. 2) There were also a number of statistically significant differences in antiviral prescribing by region for each class.

Conclusion: Phenotypic antiviral resistance for NNRTIs appears to be a major factor correlated with NNRTI prescribing. However, NRTI prescribing and NRTI resistance are both higher than PI resistance and PI prescribing, and not well correlated. Prescribing decisions may be influenced by other factors beyond resistance, including compliance, adverse events, and other considerations which will require further study.

OP 1.6.

Analysis of HIV-2 resistance to protease inhibitors

Nogueira, R.¹, Coelho, S.¹, Freitas-Vieira, A.¹,

Mammano, F.², Gonçalves, J.¹

¹- URIA - Uni dade de Retrovirologia e Doenças Infecciosas Associadas, University of Lisbon, Faculty of Pharmacy, Av. das as Forças Armadas 1600 Lisbon, Portugal

²- Laboratoire de Recherche Antivirale, INSERM U82, Paris, France

Most studies of drug-resistance mutations have been focused mainly on HIV-1. Studies on HIV-2 have been much more limited due to the low number of HIV-2 infected individuals compared to HIV-1. Moreover, HIV-2 is predominantly found in West Africa, where treatment is often not available. Overall there is little overlap sequence identity between HIV-1 and HIV-2 viral genomes. Proteases display approximately 50% identity, and their structure is highly similar. Furthermore, the susceptibility of HIV-2 to protease inhibitors (PI) is largely unknown. We have investigated in this report the possibility that the presence of genotypic changes in the protease of HIV-2 protease can be associated with resistance to PI. We studied 32 individuals infected with HIV-2 undergoing therapy with PI in order to characterize the polymorphism of protease gene in the presence of drug. The highest aminoacid variability in HIV-2 protease was predominantly observed between positions 10 and 40 and between positions 70 and 90 aminoacid. Using a resistance assay, natural susceptibility of HIV-2 primary isolates to protease inhibitors was found to be 3-4 times higher than HIV-1. In vitro selection pressure with PI showed the appearance of similar mutations to HIV-1 together with new alterations.

Protease mutations in HIV-2 were compared with similar PI-resistance mutations in HIV-1, to evaluate similarity of resistance mechanisms in these viruses. For direct mutagenesis the protease gene of HIV-2_{ROD} was used. The recombinant viral assay (RVA) was constructed by deletion of the protease gene and introduction of stop codon in the env gene of HIV-2_{ROD} clone. Intracellular recombination was achieved between the linearized HIV-2 vector and amplified protease coding regions. Resultant viruses were used to infect P4 cells expressing β -galactosidase in presence of increasing concentrations of protease-inhibitor drugs. Results show that HIV-2 can develop alterations in the protease gene that confer resistance PI. These alterations occur in similar and different positions compared to HIV-1.

OP 1.7.

Polymorphism and Drug-selected Mutations in the Protease Gene of HIV-1 in Naive and Multi-treated Patient Isolates from the Seine-Saint-Denis District in France: differences between B and non-B subtypes

Hawajri AL, Gault E, Aloui C, Drugan T, Le Gal F, Dziri-Mendil S, Dény P. Laboratoire de bactériologie, virologie - hygiène, Hôpital Avicenne, AP-HP, EA3406 ATHSCO, UFR SMBH, Université Paris 13, Bobigny, France ; University of Medicine and Pharmacy, Cluj - Romania

Phenotypic analyses of HIV-1 isolates have allowed to define anti-protease treatment algorithms which can be deduced from the amino-acid sequence of the protease gene. However, most of the collected data were obtained from HIV-1 subtype B isolates, and only few information are available concerning HIV-1 protease gene mutations in non-B subtypes. We have collected and analyzed the protease sequences of 49 naive patients (24 subtype B and 25 subtype non-B), and 530 multi-treated patients (405 [76,4%] subtype B and 125 [23,6%] subtype non-B). On the one hand, the sequences were interpreted according to Stanford "virtual phenotype algorithm". On the other hand, sequences were aligned and statistically analyzed in order to detect eventual subtype-related differences in protease sequence profiles.

In the naive group of patients, 3/49 isolates displayed anti-protease resistant mutations, either to both saquinavir and nelfinavir, or to nelfinavir only. Moreover, amino-acid substitution was significantly different between B and non-B subtypes in 8 positions of the protein, including positions 20 and 36, which are considered to be associated to drug-resistance. Finally, in 1 isolate (subtype non-B), an Asparagine was inserted at position 38 of the protease. In the multi-treated group of patients, the Stanford virtual phenotype algorithm indicated a significantly higher prevalence of anti-protease resistance in subtype B isolates than in the non-B (48% versus 36%; $p=0.016$). Analysis of the amino acid substitutions in the sequences of the protease showed that 22 positions are significantly different between B and non-B isolates. These positions included 7 sites associated to drug-resistance (10, 20, 30, 36, 50, 63, and 90), even though no significant difference of treatment exposure between B and non-B isolates was encountered. Our results indicate that the protease amino-acid substitution profile is different in B and non-B isolates and suggest that the algorithms of interpretation of the sequences to treatment strategies should be adapted to the virus subtype. They also suggest that treatment algorithms based on subtype B cohort studies might need modifications to be applied effectively on non-B subtypes isolates. Efforts should be considered to study each subtype independently.

OP 2.1. Initial Treatment Strategies

Dr. Marianne Harris and Dr. Julio Montaner
Vancouver, Canada

Recommendations concerning the timing of antiretroviral therapy initiation have undergone significant changes in recent years. These changes have been driven by growing concern over long-term toxicities of antiretroviral drugs and the consequences of chronic exposure to these agents, including their impact on cardiovascular morbidity and mortality. The strategy of deferring initial antiretroviral therapy is supported by population-based data demonstrating consistently low rates of HIV disease progression when patients commence antiretroviral therapy at CD4 cell counts of 200/mm³ or higher. Hence some international guideline panels now advise that, in asymptomatic HIV-infected patients, antiretroviral therapy can be delayed until the CD4 cell count approaches 200/mm³, without compromising the effectiveness of the treatment. In addition, there is increasing evidence to suggest that AIDS-free patients who started therapy at higher CD4 cell counts, and are currently experiencing virologic suppression and immunologic reconstitution on antiretroviral therapy, can safely interrupt therapy for many months under close monitoring. Consideration is given to restarting antiretrovirals according to the same CD4 thresholds as for initial therapy. The potential benefits of this strategy - in terms of reducing drug toxicities and costs by reducing overall exposure to antiretroviral drugs - are readily apparent; however, the long-term immunologic and clinical impact of this strategy remains to be established.

Once the need for antiretroviral therapy has been determined, a number of options exist for drug combinations that have demonstrated acceptable safety and efficacy in clinical trials. Recent data indicate that triple nucleoside regimens are a suboptimal choice for initial therapy, except in certain specific circumstances. Currently recommended treatment regimens comprise two nucleoside or nucleotide analogues plus either a nonnucleoside reverse transcriptase inhibitor (efavirenz or nevirapine) or a ritonavir-boosted protease inhibitor. For the latter, the most supporting data are presently available for lopinavir, but suitable alternatives include saquinavir, indinavir, and possibly amprenavir or atazanavir.

OP 2.2. New Anti-retroviral Strategies

Bernard Hirschel
Division des Maladies infectieuses
Hôpital Universitaire de Genève
1211 Genève Switzerland

Current HAART uses combinations of NRTIs/NNRTIs, or NRTIs/PI, or 3 NRTIs, taken daily. Once started, treatment is continued indefinitely. New strategies, currently being explored in clinical trials, include:

1) Scheduled Treatment Interruptions (STIs), for three reasons: (1) stimulation of the anti-HIV immune response, (2) reduced toxicity, and (3) reduced costs. In carefully selected patients treated mostly with PI/NRTI combinations, selection of resistant pseudospecies has not been a problem. However, hopes for immune stimulation have been dashed. Large comparative trials are ongoing to test whether there are toxicity and cost advantages to STIs.

2) Treatment with PIs only. Ritonavir-boosted PIs reach plasma levels which exceed inhibitory concentrations by several orders of magnitude. Multiple mutations are necessary before HIV becomes resistant to these high drug concentrations. PI-only therapy is being explored for drug-naïve patients (with lopinavir/r), for maintenance therapy after successful conventional HAART (indinavir/r and azatanavir/r), and for salvage therapy (lopinavir/saquinavir, and lopinavir/saquinavir/azatanavir).

3) The CCR-5 antagonists which are entering phase 2 and phase 3 trials have peculiar pharmacokinetics in that they block the receptors (or promote their disappearance from the cell surface) for a long time after administration, irrespective of plasma levels. It is therefore possible that these drugs can be administered at longer intervals, perhaps twice or once weekly.

OP 2.3. Managing Therapeutic Failure

No abstract available

OP 2.4.

HIV Resistance & Therapeutic Strategies / Résistance du VIH et Stratégies Thérapeutiques

Carlo Federico Perno, Valentina Svicher, Mariella Santoro, Caterina Gori, Roberta D'Arrigo, Maria Concetta Bellocchi, Sara Giannella, Ada Bertoli, Federica Forbici, Andrea Antinori, Francesca Ceccherini Silberstein

Dept of Experimental Medicine, University of Tor Vergata, and INMI L. Spallanzani, Roma, Italy

During its spread among humans, HIV-1 has developed an extraordinary degree of genetic diversity. Several factors are known to contribute to the generation of new viral variants and to influence the speed with which these viruses evolve: a) the error-prone nature of the RT, which lacks proofreading functions; b) the recombination between the two strands of the dimeric RNA genome, carried out by the RT enzyme during proviral DNA synthesis; c) the high rate of virus production that sustains HIV-1 infection in vivo; d) the rapid selection for viruses with different fitness, mainly due to immune pressure, co-receptor selection and antiviral therapy.

The pol region, encoding for viral enzymes such as RT and protease (PR), is subjected not only to natural variation, but also to the selection pressure imposed by the pharmacological treatment. Under these conditions, the virus is able to escape from antiviral drugs by accumulating new mutations, either alone or in clusters. The patterns of mutations accumulated by HIV under drug pressure are quite variable, depending from the level of pharmacological pressure, the backbone of virus strains, the length of therapy, etc. This makes quite difficult the definition of clear and consistent patterns of mutations associated to resistance to antiviral drugs. Indeed, with few exceptions, quantitative resistance to antivirals cannot be accurately predicted by current standard algorithms used in clinical practice.

Is the ability of HIV to mutate unlimited, depending from the type and amount of pressure given by antivirals, or are there areas of HIV-enzymes that cannot mutate without losing their functionality? This point, still unclear, has an enormous relevance in clinical practice, since it can help in designing new therapeutic strategies aimed to press the virus to mutate at key aminoacids crucial for the maintenance of sufficient viral fitness. The resulting virus may be replicating at a pace so limited that its ability to damage the immune system, as well as to further mutate to compensate such loss, is minimal.

For these reasons, we undertook a deep investigation aimed to define the conserved areas of RT and PR under pressure of antivirals. The results, presented in details in the lecture, show the presence of RT- and PR-regions highly conserved even under deep therapeutic pressure. Interestingly, such areas represent 50% and more of the total aminoacid sequences, and are distributed in long and short stretches located in various areas of both enzymes. Site-directed mutagenesis studies show that the variation of single aminoacids in these conserved areas causes a deep loss of HIV fitness, down to total inability to replicate. Further analyses show that other mutations, beyond those known to be associated with resistance to antivirals, seem to be associated with resistance to some antivirals. A confirmation of their relevance in clinical practice may help in defining more precise algorithms able to correctly predict the efficacy/resistance of antivirals.

OP 2.5.**Effects of Baseline Protease Inhibitor (PI) Mutations on the Efficacy of Ritonavir-Boosted Atazanavir (ATV/RTV) and Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Experienced Virologic Failure on Multiple HAART Regimens**M Johnson¹, E DeJesus², C Rodriguez³, L Nieto-Cisneros⁴, A Rightmire⁵, and C McLaren⁶¹Royal Free Hospital, London - England; ²IDC Research Initiative, Altamonte Springs, FL; ³Hospital Argerich, Buenos Aires - Argentina; ⁴Hospital Gabriel Mancera, IMSS, Mexico City - Mexico; ⁵Bristol-Myers Squibb Company, Hopewell, NJ; ⁶Bristol-Myers Squibb, Wallingford, CT

Background: ATV is a potent once-daily PI with durable efficacy in naïve patients and in experienced patients (when boosted with RTV). BMS AI424-045 compared the efficacy and safety of ATV boosted with RTV, or in a dual-PI regimen with saquinavir, to that of LPV/RTV as part of combination antiretroviral therapy in HIV-infected patients who had been administered at least 1 PI, NNRTI, and NRTI in 2 or more failed HAART regimens.

Methods: A post-hoc analysis was performed using the "Stanford Panel" of 16 ATV- or LPV-associated mutations (10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84, 90) to determine if the number of baseline PI mutations (<4 or ≥4) influenced antiretroviral efficacy in patients receiving ATV/RTV 300/100 mg qd or LPV/RTV 400/100 mg bid, each combined with tenofovir 300 mg qd and 1 NRTI.

Results: 48-week results are shown.

	ATV/RTV			LPV/RTV		
	Overall mutations N=120	<4 PI mutations n=80	≥4 PI n=40	Overall mutations N=123	<4 PI mutations n=76	≥4 PI n=47
HIV RNA (mean change from baseline, log ₁₀ c/mL)	-1.93	-2.13	-1.38	-1.87	-2.10	-1.47
Responders (% of patients)*	53	68	25	54	66	36

*Patients with confirmed HIV RNA<400 c/mL without intervening replicated rebounds, study discontinuations, or CDC Class C AIDS events

Virologic failure, defined as no confirmed response (HIV RNA<400 c/mL) through 48 weeks while remaining on study or a confirmed virologic rebound (HIV RNA>400 c/mL) after a confirmed response, occurred in 32 of 120 (27%) and 36 of 123 (29%) of the ATV/RTV- and the LPV/RTV-treated patients, respectively, through 48 weeks.

Conclusions: ATV 300 mg boosted with RTV 100 mg qd demonstrated efficacy similar to that of a standard of care (LPV/RTV) in treatment-experienced patients at 48 weeks regardless of the number of baseline PI mutations. The magnitude of response to treatment with either ATV/RTV or LPV/RTV was inversely related to the number of baseline PI mutations (<4 or ≥4). A comparable diminution in response was observed in both study arms in patients with ≥4 baseline PI mutations. Because of small subgroup numbers, these data should serve only as a guide to therapy decisions.

OP 3.1.
HAART-induced Immune Reconstitution: limitations & prospects

No abstract available

OP 3.2.**New Insights into Immune Reconstitution. The pleiotropic effects of IL-15**

Marie-Lise Gougeon*, Delphine Marsac#, Isabelle Liberman*

*Institut Pasteur, Molecular Medicine Department, 28 rue du Dr. Roux, 75724 Paris cedex 15, # Institute of Biomedical Sciences, Faculty of Medecine, University of Chile, Santiago, Chile.

IL-15 exhibits many activities in common with IL-2, including induction of NK cell activity and cytolytic effector cells. The overlapping biological activities of IL-15 and IL-2 are attributable to the utilization by these cytokines of two common receptor chains β and γ . NK cells are a critical component of host immune response to a variety of pathogens and they were originally identified on a functional basis because of their ability to kill certain tumor cells without previous stimulation. However, unlike T cells, they do not express clonally distributed receptors for antigen, and their function is finely regulated by a series of inhibitory or activating receptors.

The inhibitory receptors, specific for MHC class I molecules, allow NK cells to discriminate between normal cells and tumor cells (that have lost the expression of MHC class I) or virus-infected cells. Inhibitory NK cell receptors (iNKR) also regulate the function of CD8 T cells. Whether increased expression of iNKR on NK cells and CD8⁺ T cells contributes to defective antiviral activity in HIV-infected individuals is not yet clear. We have analysed the expression of iNKR (CD94, p158a, p158b and NKB1) on various cell subsets from asymptomatic untreated HIV-infected patients, patients under HAART and healthy donors. We found that HIV-infection leads to abnormal cell-surface expression of these receptors on NK cells, CD4, CD8 T cells, and $\gamma\delta$ T cells, and the up-regulation of iNKR is a consequence of HIV viremia. The influence of iNKR expression on effector functions was analysed by the detection of intracellular TNF α and IFN γ production in iNKR⁺ and iNKR⁻ subpopulations following ex-vivo stimulation with SEB for T cells or K562 for NK cells. It appeared that responding cells are mostly found in the iNKR⁻ subset, and exogenous addition of IL-15 decreases the expression of iNKR in the expressing subsets and concomitantly enhances the production of TNF- α therefore IL-15 can restore the effector functions of T cells and NK cells by modulating the expression of NKR.

Another feature of IL-15 is its ability to act as a survival factor. CD4 and CD8 T cells from HIV-infected individuals are highly susceptible to spontaneous, CD95/Fas and TNF-R-induced apoptosis, and this sensitivity may impair their ability to control HIV-infection. We reported that IL-15 exhibits a strong survival effect on total CD4 and CD8 T cells from HIV-infected individuals, and the anti-apoptotic effect of IL-15 was linked to its ability to up-regulate Bcl-2. In addition, HIV-specific CD8 T cells were found to down-regulate Bcl-2 expression, which was restored by IL-15, concomitantly with an increased survival of these cells.

In conclusion, IL-15 could affect the immune response of HIV-infected patients at different levels, first by stimulating innate immunity through the modulation of iNKR and enhancement of effector functions, and second by restoring adaptive immunity through the maintenance of HIV-specific effectors by increasing their survival. These observations could provide new implications for immune-based therapies in HIV-infection.

OP 3.3.

State of the Art of anti-HIV Immunotherapy

Giuseppe Tambussi

Clinic of Infectious Diseases

San Raffaele Scientific Institute, Milano. Italy

The advent of HAART has radically changed the clinical course of HIV infection. However, recent advances in the pathogenesis of the infection, including the analysis of T cell dynamic changes induced by the virus and HIV-1 cellular reservoirs, emphasize the fact that HIV-1 eradication will not probably occur even following a life-long use of effective antiretroviral therapy.

The vanished goal of eradicating HIV infection by combining several antiretroviral agents has refocused most of the attention on strategies aimed at the long-term management of HIV disease. Among these, immune-based interventions which include antiretroviral drugs in combination with compounds that are able to modulate the function and reactivity of the immune system might be pursued. The goal of these strategies is to achieve the long-term control of virus replication with a minimal or possibly no use of antiretroviral drugs. In this context, it is worth exploring the potential use of immune modulating drugs, such as mycophenolic acid, that thank to their mechanism of action may also exert an antiviral activity.

In this context, the possibility of combining antiviral and immune-based approaches has a solid basis in the consolidated experience of IL-2 administration. Multiple trials on different cohorts of infected individuals have shown that intermittent administration of 3-12 MIU/d of IL-2 can restore normal levels of circulating CD4+ T-lymphocytes, a crucial parameter of immune function. Retrospective analysis of individuals who have received IL-2 in previous years is encouraging in the hypothesis that the observed increases of CD4+ T-cell counts are not a simple "cosmetic" change in the composition of PBMCs of these individuals. Hopefully, ongoing phase III clinical trials will address this fundamental question. An added value of IL-2 experimental therapy is its broader implication: administration of a cytokine, a messenger protein that allows the intercellular communication among immune cells, as a drug to immunodeficient individuals may lead to the reconstitution of their immune responses, thus increasing their capacity to fight opportunistic infections and tumors.

OP 3.4. The Future of HIV Vaccine Development

Richard A. Koup, MD

While most vaccines have been developed by an empiric approach, the development of a vaccine against HIV will likely be based upon an understanding of the role of the immune system in protecting against HIV replication in infected individuals.

Development of a vaccine that stimulates neutralizing antibodies to HIV has been extremely challenging. The envelope of HIV has many ways of avoiding the affects of neutralizing antibodies, but newer approaches may get around these viral defenses. In contrast, we have made major strides in developing vaccines that stimulate CD4+ and CD8+ T cell responses against HIV. Whether these T cell vaccines will be effective in the absence of neutralizing antibodies remains to be seen.

There is reason to be optimistic that a vaccine against HIV will be able to be developed. HIV transmission is relatively inefficient, and certain aspects of the virus must be conserved in order to allow entry. In addition, there are examples of natural protection against HIV infection or disease progression. Finally, animals have been able to be protected from AIDS retrovirus infections after vaccination.

Historical methods of vaccine production include the use of attenuated viruses or whole killed virus. Because of the uniform lethality of infection with HIV, there are potential problems with both of these approaches. Newer methods of recombinant DNA technology are therefore being used to develop vaccine products that should generate both humoral and cellular immune responses against HIV. Many of these are already in various phases of clinical testing. A rational and scientific approach will hopefully lead to the development of a protective vaccine against HIV.

An initial Phase I study (VRC 004) evaluating a 4-plasmid DNA combination of B clade gag/pol/nef with envelope from clades A, B, and C has been completed in 50 healthy adults in the U.S., with no vaccine-related serious adverse events. The study evaluated doses of 2, 4, and 8 mg delivered by a needless injection device. CD4+ and CD8+ T cell responses were detected in the majority of vaccinees using peptide pools to stimulate PBMCs followed by IFN-g ELISpot and flow cytometric detection of intracellular IL-2 or IFN-g production. HIV-specific antibody response was detected in 12/40 subjects. Responses could be detected after two injections, and the responses to the 4 and 8 mg doses were greater than those to the 2 mg dose. The full immunology and development program for this vaccine will be presented.

OP 3.5.

Humoral Immune Response Monitoring in HIV-1-infected Patients under anti-Tat Therapeutic Vaccine Trials

Zagury D, Le Buanec H, Badran BM, Willard-Gallo KE, Burny A and Gallo RC

Université P et M Curie; Néovacs, 15 rue de l'Ecole de Médecine 75006 (Paris, France); ULB, (Bruxelles, Belgium); Institute of Human Virology, Baltimore - USA

The early synthesized Tat protein in its extracellular configuration exhibits pathogenic effects on both paracrine infected cells (enhancement of viral replication) (Re MC, La Placa M et al. 1995) and uninfected immunocytes (immunosuppression) (Zagury D et al., 1996 ; Cohen S, Pardee M et al., 1998; Gallo RC, 1999). To neutralize extracellular Tat and counteract its toxic effects anti-Tat therapeutic vaccines have been developed and are currently under clinical trials (Gringeri et al., 1998; Cafaro A, Ensoli B et al., 2002; Aventis Pasteur, 2002). Neutralizing anti-Tat Abs representing a major parameter to monitoring immunogenicity of the vaccine, we propose 2 functional anti-Tat Ab tests: the standard CAT assay to measure Tat-induced enhancement of viral replication and TRAIL mRNA synthesis by uninfected monocytes. Given that native Tat is unstable and some of its effects rapidly inactivated in serum, we present here standardized experimental conditions of the 2 Tat assays allowing for sensitive, quantitative and reproducible results.

OP 4.1.

Optimal use of Therapeutic Drug Monitoring in HIV Infection

David M. Burger, University Medical Center Nijmegen - the Netherlands

Therapeutic Drug Monitoring (TDM) is becoming more and more part of routine clinical practice, at least in Europe. Several studies have been published during the last years showing the benefit of using TDM to improve the management of HIV infected patients.

One of the drawbacks for using TDM in the recent past was the lack of consensus on the therapeutic range for antiretroviral drugs. Without the availability of a therapeutic range, TDM is nothing more than targeting at normal levels, without knowing whether these levels are subtherapeutic, therapeutic, or even toxic. In March of 2003, however, a consensus document was released by a group of expert HIV pharmacologists and is now available on www.HIVpharmacology.com.

Several guidelines are now more in favour of including TDM in the diagnostic make-up of new HIV infected patients. For using TDM in antiretroviral experienced patients, it is probably not enough to focus on drug levels, while no information on resistance patterns is available. The integration of pharmacological and virological parameters (the IQ concept) has been a theoretical concept for a long time, but data are now accumulating that this information can also be used in clinical practice. Finally, while the focus of TDM in the past has been on prevention of virological failure, more data are now accumulating demonstrating relationships also with toxicity. For instance, nephrotoxicity caused by indinavir, and CNS toxicity caused by efavirenz are 2 examples how TDM can be used to manage these toxicities. Limited data have become available that suggest that the same is true for hepatotoxicity due to nevirapine use, or lipid abnormalities after lopinavir use.

OP 4.2. The Search For New Antiretroviral Drugs

Erik De Clercq, Leuven - Belgium

In recent years, significant progress has been made towards the chemotherapy (and - prophylaxis) of HIV infections. This progress is situated at three different levels. (i) New anti-HIV drugs have been approved for clinical use and have entered the market: the virus entry inhibitor enfuvirtide (Fuzeon™), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (Emtriva™), the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir disoproxil fumarate (Viread™) and the HIV protease inhibitor (PI) atazanavir (Reyataz™). (ii) Other compounds have proceeded through preclinical and/or clinical development: CXCR4 antagonists (e.g. AMD070), CCR5 antagonists (e.g. SCH-C, TAK-220, and spirodiketopiperazines), NRTIs (such as amdoxovir and other 2',3' dideoxynucleoside analogues), NNRTIs (such as capravirine, dapivirine and etravirine), integrase inhibitors (such as S-1360 and other diketo acid derivatives) and PIs (such as tipranavir). (iii) Yet other compounds, acting by novel mechanisms, have recently been identified as anti-HIV agents that seem worthy of further (pre)clinical development: cell receptor CD4 downmodulators (i.e. cyclotriazadisulfonamides), viral envelope gp120 binding agents such as plant lectins and glycopeptide antibiotics (aglycons), HIV integrase inhibitors such as the pyranodipyrimidine V-165, and two new classes of compounds (i.e. N-aminoimidazoles and pyridine oxide derivatives) which seem to interfere with a post-integration, transcription transactivation event. As a whole, the approaches for the treatment of HIV infections have in recent years become both more diverse and more efficient.

OP 4.3.

New Antiretrovirals and Strategies in the Gilead Pipeline

James F. Rooney, Andrew Cheng, William A. Lee - Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404

The development of new products for the treatment and prevention of HIV infection continues to be the primary focus of research and development activities at Gilead. In an effort to reduce pill burden and increase convenience, tenofovir DF (TDF) and emtricitabine (FTC) have been combined into a single tablet, which can be taken once daily. Recent pharmacokinetic data have shown that the fixed-dose combination (FDC) of TDF / FTC is bioequivalent to the individual dosage forms. An MAA and NDA for the FDC have been filed. New compounds in development include an amidate prodrug of tenofovir, GS-7340, and a new HIV-1 protease inhibitor, GS-9005. GS-7340 is selectively metabolized inside cells, which results in accumulation of tenofovir in certain cell types, such as lymphocytes. GS-7340 is 1000 fold more active than tenofovir against HIV in cell cultures. Following 1 hour incubation of GS-7340 with whole blood, the levels of tenofovir inside PBMCs were over 20 times greater than those after incubation of whole blood with tenofovir. A Phase 1 clinical study of GS-7340 has confirmed the potent anti-HIV activity of this compound and a phase 2 study in patients with nucleoside-resistant virus is planned. Using a similar technology for targeting of lymphocytes, Gilead has developed a new HIV-1 protease inhibitor, which accumulates in lymphocytes and is highly active against viruses which contain mutations associated with protease inhibitor resistance. A phase 1 dose ranging study is underway to determine the safety, tolerability, and pharmacokinetics of this compound. New strategies for the use of current antiretrovirals include several studies exploring the potential for tenofovir DF in pre-exposure prophylaxis in patients at high risk for acquiring HIV infection.

OP 4.4.

TMC114/Tibotec/ISHEID, June 4 2004

Eric Lefebvre, Yardley - USA

TMC114 is a next generation PI with potent in vitro antiviral activity against wild-type and PI-resistant HIV-1. TMC114-C207 was an open, randomized Phase IIa study in 50 multiple PI-experienced patients. The objectives of the trial were to assess the pharmacokinetics, antiretroviral activity, safety, and tolerability of the substitution of TMC114 in a non-suppressive antiretroviral regimen.

TMC114 was co-administered with a subtherapeutic dose of ritonavir (rtv) for 14 days in multiple PI-experienced, HIV-1-infected subjects. It was substituted for the PI(s) in the non-suppressive regimen; all other ARVs were unchanged. Patients received TMC114/rtv at doses of 300/100 mg bid, 600/100 mg bid, 900/100 mg qd or continued the non-suppressive regimen. After 14 days, TMC114 was discontinued and changes in ARVs were permitted.

Median baseline plasma HIV-1 RNA for the study group was 4.3 log₁₀ and median baseline CD4 cell count was 305 cells/mm³. The median number of primary PI mutations was 3, while the median number of PI resistance-associated mutations was 6 (both primary and secondary mutations). Median change at day 14 in HIV-1 RNA was -1.38 log₁₀ for all TMC114/rtv groups and +0.02 log₁₀ for the control group. A reduction of 0.5 (or 1.0) log₁₀ in HIV-1 RNA was achieved at any time point during treatment by 97% (76%) and 25% (17%) of subjects in all TMC114/rtv and control groups, respectively.

Treatment with TMC114/rtv was generally well tolerated. Most AEs were judged to be mild to moderate in severity and no dose relationship was observed. The most commonly reported AEs were GI events (diarrhea, flatulence) and central nervous system disorders (headache, dizziness). Two subjects in the TMC114/rtv groups prematurely discontinued treatment; one due to a combination of grade 2/3 GI and a grade 3 CNS (headache) event and the other due to esophageal candidiasis and stenosis (judged as HIV-related and unrelated to TMC114/rtv). One grade 4 hepatotoxicity in a patient in the 600/100 mg bid dose group was reported as a serious AE and was judged to be probably related to TMC114/rtv. This event resolved without sequelae upon discontinuation of all antiretrovirals.

Overall, TMC114/rtv exhibited potent antiretroviral activity and favorable pharmacokinetics when given for 14 days to multiple PI-experienced patients currently receiving a non-suppressive PI-containing regimen.

OP 4.5.

The Discovery and Exploratory Development of UK-427,857: A Novel CCR5 Antagonist for the Treatment of HIV

C. A. Hitchcock, Pfizer Global Research and Development, Sandwich Laboratories, Sandwich CT13 9NJ, UK

The successful future management of patients infected with HIV requires the discovery and development of new agents that combine novel mechanism-of-action with pharmacokinetic, safety and toleration profiles that are consistent with chronic, durable therapy. It is against this backdrop, that the inhibition of HIV fusion and entry into immune function cells is one of the most promising approaches to discovering new classes of anti-retroviral agents that have the potential to meet the aforementioned target profile.

UK-427,857 is a novel CCR5 antagonist and is the most advanced clinical candidate in Pfizer's CCR5 discovery and development programme. UK-427,857 is exquisitely selective for the CCR5 receptor and inhibits viral replication by blocking the binding of viral gp-120 to the CCR5 receptor. This translates to potent activity in vitro against both lab-adapted and primary clinical HIV isolates spanning all of the clades, including viruses that are resistant to current classes of HIV agents.

UK-427,857 has been evaluated in >400 volunteers and HIV patients where it is well tolerated at doses in excess of those required to block the CCR5 receptor and those providing free drug levels above the in vitro concentrations for potent antiviral activity. Consistent with this, UK-427,857 has demonstrated encouraging short-term (10 day), single agent efficacy as measured by reductions in viral loads in asymptomatic HIV patients; CCR5-tropic patients receiving 100mg BID showed a mean decrease in viral load of 1.42log₁₀ from baseline to day 11, whereas a dose of 25mg QD produced a mean viral load reduction of 0.42log₁₀.

The clinical pharmacology of UK-427,857 has been studied extensively in volunteers. It is a substrate for cytochrome P-450 3A4 (CYP 3A4) and the p-glycoprotein transporter, but it does not significantly inhibit or induce CYP P-450 3A4 or other cytochrome P-450 enzymes. Studies both with CYP 3A4 inhibitors and inducers have demonstrated that UK-427,857 will have manageable drug interactions when used in the setting of HIV patients receiving current HAART.

In summary, UK-427,857 is a novel CCR5 antagonist with potency, pharmacokinetic and toleration profiles that merit its further evaluation as a new therapy for patients with HIV/AIDS.

OP 4.6.

BMS-488043: A novel, small-molecule HIV-1 attachment inhibitor

R. Colunno, H. Ho, N. Zhou, T. Masterson, G. Hanna, J. Kadow and P-F Lin
Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA

The recently discovered HIV-1 Attachment Inhibitors (AIs) induce conformational changes within the viral envelope gp120 protein and inhibit attachment to cellular CD4 receptors. Potent and selective inhibition is observed in vitro against macrophage-, T-, and dual-tropic HIV-1 strains. Consistent with our previous results, a series of biochemical studies show that AIs such as BMS-488043 and BMS-378806, prevent sCD4 binding to gp120. AIs bound readily to gp120, but could not bind to or displace sCD4 from pre-formed gp120/sCD4 complexes. Compound inhibition was greatly reduced with increasing concentrations of sCD4 in a gp120/CD4 binding ELISA assay. Collectively, these results indicate that AIs function by blocking gp120/CD4 interaction and that binding of AIs and sCD4 to gp120 is mutually exclusive. Mapping studies show that deletions of V1, V2 and V3 loops had a significant impact on AI binding. Circular dichroism spectrum shifts, changes in the rate of thrombin cleavage of the V3 loop when AIs are bound, and significant decreases in the binding of CD4i and CD4BS MAbs to gp120 upon AI binding confirmed that AIs induce gp120 conformational changes when bound. Phenotypic and genotypic analysis of drug selected virus variants showed that selected resistance substitutions span the viral envelope, with at least 9 residues identified at CD4 specific contact sites. These data are consistent with compounds sharing interaction sites with CD4 and binding to a pre-CD4 form of gp120.

The antiviral activity, safety, and tolerability of AI BMS-488043 were evaluated in a placebo-controlled ascending multiple-dose study in HIV-1-infected adults. Oral administration of 800 or 1800 mg doses vs. placebo q12 hr for 8 days were evaluated over a 14 day period with daily viral load (VL) monitoring. In subjects receiving the 1800-mg dose of AI BMS-488043, 67% (8/12) had a VL decline $>1.0 \log_{10}$, with 42% (5/12) having a VL decline $>1.5 \log_{10}$. None of the placebo treated subjects exhibited a VL drop of $0.4 \log_{10}$. BMS-488043 was well tolerated and there were no serious adverse events and no discontinuations from the study. This proof-of-concept study validates the AIs as a novel class of antiretrovirals with potent antiviral activity in HIV-1-infected subjects. Further development of AIs are clearly warranted.

OP 4.7.**Identification and characterization of the determinants of activity of the HIV-1 maturation inhibitor PA-457**

F. Li¹, D. Zoumplis¹, C. Matallana¹, C.S. Adamson²,
N.R. Kilgore¹, M. Reddick¹, G. P. Allaway¹, D. E. Martin¹,
E. O. Freed² and C. T. Wild¹.

¹Panacos Pharmaceuticals, Gaithersburg, MD.

²National Cancer Institute, Frederick, MD.

We have previously demonstrated that the betulinic acid derivative, PA-457, potently inhibits HIV-1 replication by targeting a late step in Gag processing (Li, et al., Proc Natl Acad Sci U S A. 11:13555-13560, 2003). Specifically, PA-457 blocks the conversion of the capsid precursor (CA-SP1, p25) to mature capsid protein (CA, p24) resulting in the release of immature, non-infectious viral particles. Consistent with this novel mechanism of action, PA-457 retains activity against virus isolates resistant to the currently approved classes of HIV therapeutics. Results from in vitro selection experiments indicate that determinants of PA-457 activity reside in the region flanking the Gag CA-SP1 cleavage site. This presentation will describe our efforts to identify and characterize the molecular determinants of PA-457 activity.

OP 4.8.

Pharmacological Evaluation of SPD754, a New NRTI

R Bethell, Shire Biochem Inc., Laval - Canada.

Background: SPD754 is a deoxycytidine analogue (dCA). The pharmacokinetics (PK) of both SPD754 in plasma and SPD754-triphosphate (SDP754-TP) in PBMCs have been shown to be linear across a range of doses up to 800mg bd in man. 10 days monotherapy with 1200mg/day (600mg bd or 1200mg qd) in treatment naive patients resulted in a 1.65 log₁₀ mean reduction in HIV-1 RNA. M184V confers a median 1.8-fold change in susceptibility to SPD754. The addition of up to 5 TAMs also confers a median 1.8-fold change. SPD754 is therefore likely to be effective for the treatment of both ART naïve and experienced patients. SPD754 and 3TC have additive antiviral activity against wild-type HIV-1 in vitro but, in common with other dCAs, share a common intracellular anabolic pathway. The effects of SPD754 and 3TC on each other's intracellular phosphorylation were investigated in vitro, as was the influence of 3TC on the antiviral activity of SPD754. 3TC and SPD754 were administered to human volunteers alone or in combination to determine the PK profiles the parent compounds in plasma and of their intracellular TPs in PBMCs.

Methods: PBMCs were incubated in vitro in the presence of fixed concentrations of [³H]SPD754 and unlabelled 3TC, or [³H]3TC and unlabelled SPD754. Intracellular concentrations of labeled phosphorylated metabolites were determined by HPLC. The antiviral activity of SPD754 against a recombinant HIV-1 containing the M184V mutation was assessed in activated PBMCs at a range of 3TC concentrations. In the human volunteer study, 21 male HIV-ve subjects received either SPD754 600mg bd, 3TC 300mg qd or both in random order for 4 days (with ≥7 day washout). Extensive PBMC and plasma sampling was undertaken after the final dose in each period. Parent plasma and intracellular TP concentrations were assayed by HPLC.

Results: The entry of SPD754 and 3TC into PBMCs was unaffected by each other's presence. 3TC reduced intracellular SPD754-TP concentrations in a dose dependent manner, with 3μM 3TC reducing SPD754-TP by 4-6 fold relative to its concentration determined in the absence of 3TC. SPD754 had no effect on intracellular 3TC-TP concentrations. The IC₅₀ value of SPD754 against M184V HIV-1 was increased 2-4 fold by the addition of 3TC. The human plasma PK of SPD754 and 3TC, and the intracellular PK of 3TC-TP, were un affected by co-administration. In contrast, intracellular SPD754-TP concentrations were reduced approximately six-fold in the presence of 3TC.

Conclusions: Evaluation of the intracellular TP concentrations of NRTIs in combination is essential as plasma PK studies may not predict intracellular effects. SPD754 has promising antiviral activity against viruses harboring M184V and multiple TAMs. However the marked reduction in intracellular SPD754-TP concentrations in the presence of 3TC, resulting in antagonism of their antiviral activity, indicates their co-administration, and potentially that of other dCAs, is likely to be unsuitable for clinical practice.

OP 5.1.

Management of metabolic complications of antiretroviral therapy

Morrie Schambelan, MD

Div of Endocrinology, University of California San Francisco, San Francisco, CA.

The past several years have witnessed a dramatic reduction in HIV-associated morbidity and mortality in the developed world, an event that is generally attributed to the advent of highly active antiretroviral therapy (HAART). However, the enthusiasm generated by this therapeutic advance has been tempered by widespread reports of potentially deleterious metabolic side effects, including insulin resistance, dyslipidemia, and changes in body fat distribution that include syndromes of both fat accumulation (visceral adiposity, buffalo hump) and fat loss (lipoatrophy). Studies performed in large cohorts in countries with widespread access to HAART suggest that nearly 50% of individuals develop the morphologic features of this syndrome. Given the similarity to metabolic syndrome X, which has been associated with increased risk of cardiovascular disease, it is feared that these side effects may impact on the long-term prognosis in patients whose life expectancies have been significantly extended due to effective viral suppression by HAART. This presentation will focus on current treatment options for the so-called lipodystrophy syndrome including: changes in the antiretroviral regimen (e.g. PI-sparing regimens, alterations in the nucleoside backbone); cardiovascular risk reduction with lipid-lowering agents (e.g. statins, fibrates) and life-style modification (e.g. diet and exercise); insulin-sensitizing agents (e.g. metformin, thiazolidinediones); and lipolytic agents (e.g. recombinant human growth hormone). The theoretical basis for and preliminary data supporting evaluation of experimental therapies (e.g. recombinant human leptin, recombinant human insulin-like growth factor I) will also be discussed.

OP 5.2. Update on HAART-induced lipodystrophy

Jacqueline Capeau

INSERM U402, Faculty of Medicine Saint-Antoine and Tenon Hospital - University Pierre and Marie Curie, Paris

The lipodystrophy syndrome frequently observed in HIV-infected patients often associates peripheral lipoatrophy, central hypertrophy and metabolic disorders but this set of alterations is not always present. In addition to factors related to the infection and to the patient, the treatment plays a major role in the occurrence of these alterations. Clinical data suggest that NRTI therapy is associated with peripheral lipoatrophy while treatment with PI increases the severity of lipodystrophy and of metabolic disorders.

To better approach the pathophysiology of the drug effects, *in vitro* adipocyte cell-models were used. An short-term inhibitory effect of PI on glucose transport was reported by the group of Mueckler. In long-term conditions, we observed that thymidine analogues, d4T and ZDV, contrary to other NRTI, can alter mitochondrial functions. Some PI but not all were able to strongly affect adipocyte differentiation possibly by targeting the step of the adipogenic differentiation factor SREBP-1. This could result from an altered structure of the nuclear lamina network due to impaired maturation of the lamina protein, lamin A. Thymidine analogues did not impair adipocyte differentiation but altered adipocyte lipid content. PI, contrary to NRTI, induced insulin resistance. Finally, some PI and thymidine analogues markedly altered adipocytokine expression and secretion : while IL-6 and TNF α were increased by the drugs, adiponectin was decreased. The altered secretion of IL-6 and TNF α was parallel to the extent of drug induced-apoptosis. Thus, *in vitro*, NRTI and PI could alter different adipocyte functions and could act in synergy to induce lipid loss and apoptosis ultimately leading to fat loss.

In vivo studies revealed that NRTI could play an important role in lipoatrophy not only by decreasing mitochondrial DNA but also by other mechanisms. Lipoatrophic adipose tissue from patients presented major histological alterations with decreased adipocyte size, increased fibrosis and macrophage infiltration. This tissue had an altered differentiation and insulin sensitivity. The profile of adipocytokines was markedly altered with increased TNF α and IL6 and decreased adiponectin and leptin expression. In addition, as *in vitro*, expression of TNF α and IL6 was parallel to the level of cell apoptosis suggesting that these cytokines play an important role in fat loss. These data, together with *in vitro* data, suggest that ART-induced lipoatrophy could result from the synergistic effect of NRTI and PI which could alter adipogenic transcription factors, adipocytokine secretion, mitochondrial function resulting in decreased differentiation, adipose insulin resistance and apoptosis ultimately leading to lipoatrophy. Visceral fat hypertrophy could be explained by the different physiology of visceral adipocytes which could become hypertrophied due to increased local cortisol synthesis.

Metabolic alterations observed in ART-treated patients could result from the direct effect of drugs on lipid metabolism or insulin sensitivity. In addition, due to lipodystrophy, adipose tissue has an altered pattern of adipocytokine secretion with decreased adiponectin and an increased release of free fatty acids. This with aggravate metabolic disorders and insulin resistance.

OP 5.3.**In vitro Suppression of the Lipogenic Pathway by the non-nucleoside Reverse Transcriptase Inhibitor Efavirenz in 3T3 and Human Preadipocytes or Adipocytes**

El Hadri K, Glorian M, Monsempe C, Dieudonné MN, Pecquery R, Giudicelli Y, Andreani M, Dugail I, Fève B. UMR CNRS 7079, Paris - France

A serious metabolic syndrome combining insulin-resistance, dyslipidemia, central adiposity, and peripheral lipoatrophy has arisen in HIV-infected patients receiving highly-active antiretroviral therapy. The aim of this work was to examine the effects of the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz on adipocyte differentiation and metabolism. When induced to differentiate in the presence of efavirenz (5-50 μ M), 3T3-F442A preadipocytes failed to accumulate cytoplasmic triacylglycerol droplets. This phenomenon was rapidly reversible, and was also readily detectable in the 3T3-L1 preadipocyte cell line, and in primary cultures of human preadipocytes. When applied to mature 3T3-F442A adipocytes, efavirenz induced a delayed and moderate reduction in cell triglyceride content. Measurement of [3 H]-deoxyGlucose uptake, basal and agonist-stimulated lipolysis, and cell viability indicated that these pathways are not involved in efavirenz effects on triacylglycerol accumulation. By contrast, we found that the NNRTI induced a dramatic dose- and time-dependent decrease in gene and protein expression of the lipogenic transcription factor sterol regulatory element-binding protein-1c (SREBP-1c). Adipose conversion was only altered at the highest efavirenz concentrations, as suggested by the mild reduction in peroxisome proliferator-activated receptor- γ and CCAAT/enhancer-binding protein- α . CCAAT/enhancer-binding protein-13 remained unchanged. The inhibition of SREBP-1c expression was accompanied by a sharp reduction in the expression of SREBP-1c target genes, and in the adipocyte lipogenic activity in efavirenz-treated cells. Finally, the inhibitory effect of efavirenz on cell triglyceride accumulation was prevented by directly providing free fatty acids to the cells, and was reversed by overexpression of a dominant positive form of SREBP-1c, reinforcing the implication of this transcription factor in the anti-lipogenic effect of the drug. When considered together, these results demonstrate for the first time that the NNRTI efavirenz induces a strong inhibition of the SREBP-1c-dependent lipogenic pathway that might contribute to adipose tissue atrophy (J Biol Chem, in press).

OP 6.1.
HIV in Central & Eastern Europe

No abstract available

OP 6.2.

Family Systems Psychotherapy for Substance Abuse, HIV Care

Natalia Vlasova

ICO "Steps", Vinnitsa branch, Ukraine

Vinnitsa Branch of International Charity Organization "Steps"

34/10 Petra Zaporogtsa str., Vinnitsa 21001 - Ukraine

Ph : +38 (0432) 35-37-51; 26-41-05 -

Email : vsteps@in.vn.ua

For last years chemical dependence, HIV acquired the epidemic range in Ukraine and in Vinnitsa oblast in particular. Statistics data certify from 189686 persons have formed the population of Vinnitsa oblast there are 23027 persons with alcohol abuse, 1134 with drug and 27 with toxic had been registered officially. So this quantity is larger to a great extent. Each 100-th citizen of Ukraine is HIV-infected. Medical establishments are engaged in physical symptoms of chemical dependence elimination, but mental, psychological sphere has been the core of dependence is almost out of physicians' field of vision. And different non-medicament psychological rehabilitation programmes, necessity and importance are obvious. Rehabilitation Center "Steps" over-all approach to the problem provides for psychotherapy of the family members without fail. Such approach is more effective as the practice displayed.

If the substance abuse and/or HIV is regarded as the whole family symptom, substance abuse, HIV care approach from family system direction point of view makes psychological problems of the substance abuse, HIV dysfunctional family more explicit and the psychotherapy of substance abuse and co-dependence becomes more effective.

Family is the open developed system has functioned due to interrelationship action of two laws - the law of homeostasis maintenance and the law of homeostasis divergence. The family is open system (if it is healthy), and the members interact with each other and with surrounding systems (school, business, science, religion, state etc.). The family as the system has the following peculiarities:

- System as the whole is larger than the sum of its parts;
- Something has affected the system in the whole influences on each individual element inside the system;
- The affect or change in the state of one of the system part is reflected in the other parts of the system in the whole changing.

Main positions of the family approach in psychotherapy of substance abuse are the following.

- Family members are closely linked with each other and fix in their relations those alterations and aims have made for the problem behaviour appearance instead of each of the family member growth and development.
- The vital system is described with mutability (from entropy up to rigidity) with respect to large complex of stable, repeated pictures of interaction (stereotypes). Those pictures of interaction, behavior and aims can be interpreted as linear (while relations of cause and effect are fixed) or circulated (while the symptom and the problems in the family are in interrelationship, in the circulated sequence of events determination have influenced mutually on each member of the family).
- Family problems are often linked with adaptation dilemmas to some surroundings influence and alterations (horizontal stress factors). Those alterations can occur when one of the family members starts the abuse. Such fact can force the family to refuse from old stereotypes and to create new relations.

Healthy and "problematic" members of the family have the chance to display various types of reaction on feedback with the environment. And the feedback means the necessary for the adaptation changes system answer. Adaptation can be displayed in the alteration refusal. Dysfunctional family on the early stage of the substance abuse does not remark the abuse of one of the family members or excuses him, defends from reprimand or entourage negative attitude and so, the person with substance abuse problem delegates responsibility of the abuse to the family members who take upon such state of affairs. Members of the harmonious family react quickly and coincidentally to the internal and exterior situation. The feedback reaction is positive alterations in the family, the restoration and spontaneity and creativeness growth of the family members.

- From the system point of view alterations are not the one and only decision of the sole problem (stop the abuse and there will be no problems in the family), but the dilemma which needs the solution. The substance abuse family psychotherapy question of principle lies not in the symptom (substance abuse, HIV) deliverance, but what will happen in the case of its deliverance. The accent is transferred from the discussion of the problem who is the "symptom bearer", where is its reason and how to get out of on the problem how the family will function without it and what is the cost of its elimination.

Substance abuse family is dysfunctional; rigid family system has attempted to remain habitual stereotypes of interaction between the elements of own subsystems and another systems out of exterior conditions alterations dependence. So topical necessities îf the weakest family member, the substance abuse person are blockaded and the substance abuse problem makes progress. He becomes "the symptom bearer", has been able to afford old fully formed interrelations between the family members.

"Identified patient" is the member of the family, divergent behavior and psychological (substance abuse, HIV) problems of who are the direct ground of the family appeal to psychotherapeutic aid. "Identified patient" destroys rigid family rules. The psycho-therapeutic efficiency result is morphogenetic function - positive feedback, divergences to the side of family system variations intensification the goal of which is family system alterations and transition to the next stage. The main factor has led to positive an alteration in the family is despair. "If the family is in despair it changes if not it remains the former" (C. Vitacker).

OP 6.3. HIV Infection in Estonia

Dr Anneli Uuskula

Department of Public Health, Department of Dermatology, University of Tartu, Ravila 19, Tartu 50411
- Estonia

HIV infection associated with injecting drug use has been reported worldwide, and is established as the major cause of rapidly increased rates of HIV infection in several countries throughout Eastern Europe. In the newly independent states, large-scale HIV epidemics have been observed from 1995 onward, after introduction to injecting drug use (IDU) communities.

The number of HIV infected cases remained relatively low, despite the rapidly and substantially increasing sexually transmitted diseases (STD) rates (syphilis in particular) - the HIV epidemic began to develop only after it was introduced into the drug injecting community. Through 1999, only 96 cases of HIV had been reported nationally. The HIV epidemic has progressed since 1999 with: 390, 1474, 899 and 840 new HIV positive cases were reported in years 2000, 2001, 2002, 2003 respectively. According to the UNAIDS, an estimated 1% of the young adult population (aged 15-49) in Estonia are living with HIV infection - the highest estimates in Eastern Europe.

HIV infection is predominant in the IDU population; thus providing the most common route of HIV transmission to the general population -- a critical concern. As has been noted in other settings, IDU acquired HIV often serves as the conduit for the introduction of infection into the heterosexual non-drug using population. The dramatic increase of IDU acquired HIV infection with corresponding rates of STDs places the Baltics, high rates of sex risk behavior and inadequate knowledge regarding prevention of disease transmission places Estonia at high risk for an impending sexually and STD driven HIV epidemic.

OP 6.4. Spread of the HIV/AIDS infection and STIs in the Slovak republic

Assoc.Prof. Emil Tomášik, MD., PhD

Public Health Authority of the Slovak Republic

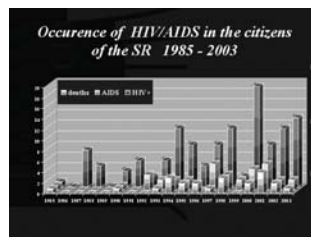
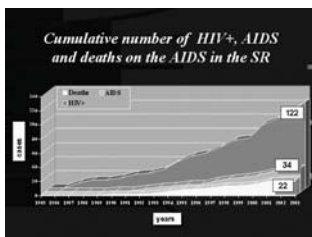
Department of STI prevention and coordination centre of HIV/AIDS

Slovak republic belongs to the countries with a very low incidence of the spread of HIV/AIDS infection and STIs. We would like to believe that this situation is a result of the good and correct administration of the preventive measurements. This prevention in our country has a very long tradition.

The surveillance of HIV/AIDS infection began in the Slovak Republic early in the 80-ies last century. The NRC for HIV/AIDS infection was established in the 1984. The first regulation about the HIV/AIDS prevention was published in the 1988. In this time in our country exists the National committee of the HIV/AIDS prevention and the National program of the HIV/AIDS infection in SR.. The activities in the HIV/AIDS and STI prevention are coordinate by our institution.

Since the beginning till now were performed more than 3,5 million tests. In the last year were performed more the 150 000 examinations, but the count of these examinations has a decreasing trend.

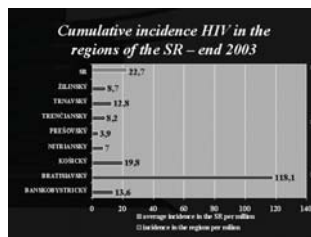
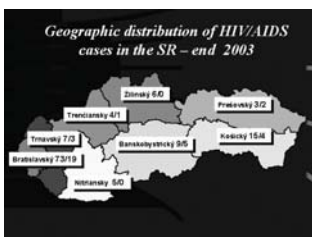
The exact monitoring of this infection in SR began in the 1985. The cumulative number of registered HIV infections up to now is 122 cases. The clinical AIDS diseases developed in the 34 persons and 22 patients died.



This graph shows the dynamic of the spread of the HIV infection, AIDS and deaths in the individual years. Increasing is variable and it is a favorable situation, that means that the dynamic of increase is not constant.

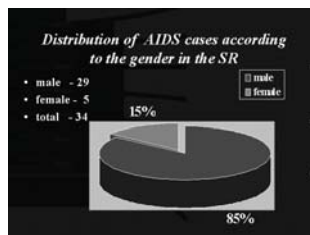
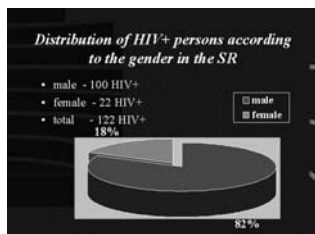
The spread of the HIV/AIDS infection in the individual regions of the Slovakia clearly shows that the occurrence is the highest in the big agglomeration with the higher tourist traffic.

The highest concentration of the HIV infection and AIDS cases is in the capital Bratislava and its region. Second highest occurrence is in the Košice region in the east of the Slovakia.



The average cumulative incidence per 1 million citizen in the SR is 22,7/1 000 000. The highest incidence is in the Bratislava region and this value is more than 5-times higher as the average. In the all rest regions the incidence is lower than the average value.

The majority of the HIV positive cases 82% are the men and the same situation is in the spread of AIDS disease 85%.

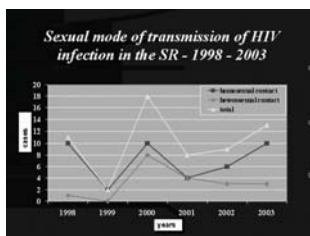
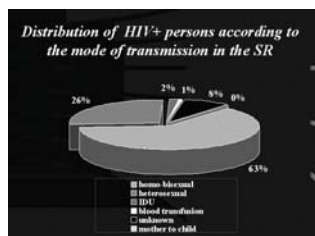


The next figure shows the distribution of the HIV positive cases according to the mode of transmission. The most frequent mode of transmission is the sexual contact. Nearly 89% from the all transmissions were caused through the sexual intercourses. From the sexual mode of transmission almost 72% creates transmission by the sexual intercourse in the group men who have sex with men.

The mode of transmission by blood transfusion was observed only in one case, by the blood transfusion abroad our country.

Relative favorable situation is in the group of the IDU-s. We have 2% of this mode of transmission only. In our country exist good preventive programmes in this risks group.

It is necessary to show the fact that the mode of transmission from mother to child was not registered despite of the deliveries of the HIV positive women. In the age-group 0-14 years does occur no case of HIV positivity. The most of HIV positive cases exist in the age-group 20-34 years 62%.

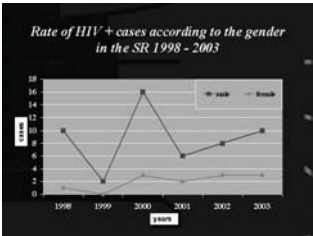
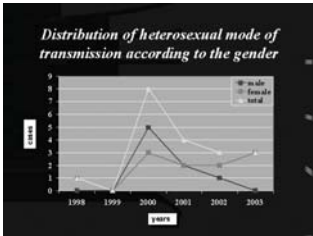


Analysis of the sexual mode of transmission shows that in our country dominates the transmission by the sexual intercourses between the men who have sex with men and its ratio has an increasing tendency, and on the contrary the ratio of the transmission by heterosexual intercourses goes down.

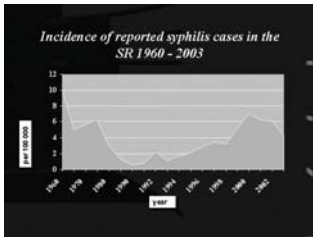
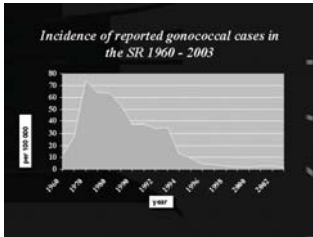
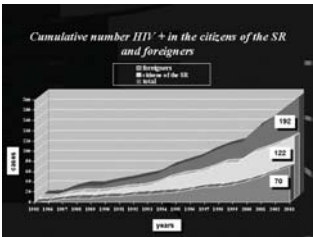
Analysis of the heterosexual mode of transmission shows that this mode of transmission is more frequent at the women than at the men.

We can allege that in the period last 5 years the trend of the growth the number of the new infected people is not changed and the men dominate.

The big problem is a migration of the foreigners. The number of HIV positive persons who were detected in our country is 70.



The situation about the STI is very similar to the situation in the neighbourly ountries. We can notice the growth of the syphilis and decrease in the gonococcal infections. But I have to remark that there is the situation in the reported cases.



OP 6.5.**The incidence of viral hepatitis markers among romanian teenagers with long-lasting horizontally acquired HIV infection**

¹Institute of Virology, Bucharest, Romania; ²Municipal Hospital, Constanta, Romania, ³Baylor College of Medicine, Houston, TX

We studied the frequency of viral hepatitis markers in a sample of 161 Romanian teenagers' patients, mean age 13.9 years (standard deviation=1.2) with more than ten years long-lasting HIV infection, but without clinical or biochemical signs of liver disease. All the participants have horizontally acquired chronic HIV infection and 69% were under antiretroviral therapy. 126 patients (78.2%) were in CDC clinical stage B and only 35 in stage C. Overall, 126 (78.3%) children have markers of HBV infection (anti HBc positive) and 9 (5.6%) were anti HDV coinfecting; only 3 (1.86%) have anti HCV antibody. A high prevalence of HBV replicative markers was found: 70 patients (43.5%; 95% CI=36.1-51.2) were HBsAg positive; 18 (11.2%; 95% CI=7-17) were HBeAg positive; while only 31 (19.2%; 95% CI=13.9-26.1) cleared the infection being antiHBs positive. To see the influence of advanced HIV infection on the evolution of HBV co infection we split the lot in two groups according with their immunological status. The prevalence of HBs antigenemia was 56.1% in severe immunodepressed children (CD4+ cells number <200) versus 36.5% in those with >200 CD4 cells ($p=0.02$), suggesting that the degree of immunosuppression is correlated with the persistence of HBV replicative markers. The presence of HBV DNA was tested in all 32 HBsAg positive immunodepressed patients. Unexpectedly, 19 (59.4%) of these had undetectable levels of the replicative marker (<1000 copies/ml) and 13 have high viremic samples (>107 HBV DNA copies/ml). This finding supports the ideas that HBV is preferentially hepatotropic, but not directly cytopathic and that an efficient cellular immune response does not necessarily determine a favourable outcome even in the context of HBV/HIV co-infection.

OP 7.1.

Treatment of HIV-HBV Coinfection

Treatment of chronic HBV infection in HIV infected patients.

Yves Benhamou

Chronic infection with hepatitis B virus (HBV) affects about 5% of the world population. Among human immunodeficiency virus (HIV) infected individuals, the prevalence of chronic hepatitis B is 10 fold higher (10%) than in the general population. HIV/HBV co-infected patients have an increased risk of cirrhosis and liver-related death compared to HBV mono-infected patients. Due to the complex and potent interactions between HBV and HIV, as well as with the immune system and antiretroviral therapy, the strategy and management of anti-HBV therapy in HIV-infected persons must take into consideration both viral infections.

Lamivudine (LAM) is effective against both HIV and HBV replication. Among HIV/HBV co-infected patients, LAM (150 mg bid), given for HIV infection as part of an antiretroviral regimen, promptly inhibits HBV replication. However, HBV resistance to LAM (LAM-R) is observed in 50% and 90% of the cases after 2 and 4 years of therapy, respectively. The efficacy of adefovir dipivoxil (ADV) in HBV infected/HIV negative patients has been demonstrated against wild type, pre-core and LAM-R HBV. ADV has been shown to be effective and well tolerated in the treatment of LAM-HBV in HIV/HB co-infected patients. Four years of ADV in LAM-R HBV/HIV coinfectd patients resulted in continuous decline of serum HBV DNA, with no mutation related resistance of both HBV DNA and HIV RNA reverse transcriptase. Tenofovir disoproxil fumarate (TDF) has recently been shown to have significant activity in HIV/HBV co-infected patients. TDF is approved for HIV infection and had shown to inhibit replication of wild type, pre-core and LAM-R HBV. Emtricitabine (FTC) has been also recently approved for the treatment of HIV infection. In recent studies FTC has demonstrated activity against wild type and pre-core HBV in both HBV mono-infected and HIV/HBV co-infected patients. Nucleotides and nucleosides (NUCs) therapies are both effective for the control of HBV replication. LAM is associated with a high rate of HBV resistance. However, these treatments are associated with a low rate of HBe seroconversion. Combination therapy with NUCs may prevent HBV resistance. Although, no resistance to ADV was observed after 4 years of therapy when ADV was added to LAM. Combination therapies with pegylated interferon and NUCs may increased the seroconversion rate and are under investigation.

In summary, anti-HBV therapy should be considered in HIV coinfectd patients who require anti-retroviral therapy. In patients with chronic hepatitis B who do not need anti-HIV therapy, AD therapy should be proposed.

OP 7.2.

Treatment of hepatitis C in HIV-coinfected patients

Vincente Soriano

Hospital Carlos III, Madrid, Spain

Chronic hepatitis C affects one third of HIV-positive persons in Europe, but prevalence rises to >75% among IDUs. Progression to cirrhosis occurs faster and hepatocarcinoma may appear at younger age in this population. Chronic HCV infection increases the risk of liver toxicity using ARV drugs and may compromise immune recovery after beginning HAART. Guidelines for the management of chronic hepatitis C in the setting of HIV infection already have been published (International Panel. AIDS 2004;18:1-12).

The best candidates for anti-HCV therapy are HIV-positive subjects with proven chronic hepatitis C (positive HCV-RNA and elevated ALT), having CD4 counts >300 cells/mL and low plasma HIV-RNA (<10,000 copies/mL), with or without ARV therapy.

The combination of pegylated interferon (IFN) plus ribavirin (RBV) is the best choice of anti-HCV therapy, at doses used in HIV-negative individuals. However, early, end-of-treatment and sustained response rates are lower in HIV-positive patients than in HIV-negative counterparts. The results of two large trials (RIBAVIC and APRICOT) have been recently released and will be discussed in detail.

Quantitative monitoring of the virologic response to anti-HCV therapy seems to be useful in patient management. Patients that achieve a reduction in plasma HCV-RNA >2 logs at week 12 of treatment may benefit from continued therapy. For those who did not reduce HCV-RNA >2 logs at 12 weeks, the chance of cure is negligible, and thus treatment can be stopped. Patients with detectable HCV-RNA at 24 weeks of treatment may be also considered as failures, and discontinue therapy.

There is no evidence of any benefit from increasing the doses of either IFN and/or RBV in induction protocols. Extending treatment from 6 to 12 months in subjects with HCV genotypes 2 and 3 who had an early virologic response may increase their sustained response rate. Patients with HCV genotypes 1 and 4 with early virologic response should be treated for at least 12 months.

The risk of interactions between RBV and some NRTIs is of great concern. In particular, ddI should be avoided, due to the higher risk of hyperlactatemia and/or pancreatitis. AZT should also be used with caution due to the higher risk of anemia.

Finally, compliance with the medication should be strongly encouraged. In the face of mild side effects, managing these appropriately and/or reducing doses of either IFN or RBV would be preferable to stopping therapy.

OP 7.3.**Tolerance of Viral Hepatitis Therapy in HIV-infected Patients**

No abstract available

OP 7.4.**Role of the hepatitis C virus-coinfection on humoral immune alterations in HIV-infected patients on HAART**

Natalia Soriano-Sarabia, Sonia Molina-Pinelo, Carmen Delgado-Pecellin, Beatriz de Felipe, Armando Sanchez-Quijano, Eduardo Lissen, Manuel Leal, Alejandro Vallejo
Group for the Study of Viral Hepatitis and AIDS, Hospital Universitario Virgen del Rocío, Seville, Spain

Objectives: Since the introduction of HAART the interest in humoral immunity alterations that induces chronic aberrant activation and immunodeficiency has risen. Our first aim was to analyze factors involved in both B cell count and B cell function disorders before the initiation of HAART in a closely followed cohort of 72 HIV-infected and naïve patients. Our second aim was to analyze long-term influence of HCV coinfection (N=35) in reverting these alterations in the same cohort after 156 weeks on HAART.

Results: Before the initiation of HAART, HIV-infected patients showed B lymphopenia and polyclonal hypergammaglobulinemia compared to HIV-uninfected individuals ($p<0.001$). When this cohort of patients was analyzed according to HCV infection, no statistical differences in CD19, CD4 cell count and CD21low expression were found; instead IgG levels in HCV-coinfected patients were significantly greater than those found in HCV-uninfected patients ($p=0.001$). Moreover, beta-2

-microglobulin level was higher among HCV-coinfected group compared to HIV-only infected patients ($p=0.03$). Besides, a strong negative correlation ($p=0.005$) between CD19 cell count and circulating IgG levels was found at baseline in the total of HIV-infected patients. This correlation was significant only among HCV-coinfected patients ($p=0.005$). During HAART, B lymphopenia and hypergammaglobulinemia slowly started to revert. At week 156 of treatment, normal values of CD19 cell counts were achieved, and although IgG levels were still increased compared to uninfected controls, they tended to normalize. Nevertheless, HCV-uninfected patients almost achieved normal CD19 cell counts and IgG levels after 156 weeks on HAART, while the HCV-coinfected group did not achieve normal values neither in B-cell counts nor in circulating IgG levels. Beta-2-microglobulin achieved normal values at week 12 after treatment among HCV-uninfected patients, while HCV-coinfected patients did it at week 48. After 60 weeks of treatment, levels of CD21low cells significantly decreased in the total HIV-infected patients ($p=0.003$), as well as among HCV-uninfected ($p=0.037$) and HCV-coinfected group ($p=0.028$).

Discussion: B cell lymphopenia at baseline may be explained by inhibition of naïve B cell proliferation by antigen:antibody complexes feedback regulation, massive differentiation into plasma cells, and also because immature precursors may be sequestered in bone marrow and lymph nodes. Basal correlation between CD19 cell counts and plasma IgG levels in the total HIV-infected patients was due to the presence of HCV. Thus, HCV activates B cells that proliferate and differentiate into antibody-secreting cells. Humoral immune system was chronically activated in HCV-coinfected patients and showed a delay in the recovery of normal humoral immune function because B cells have to differentiate into antibody-secreting cells in order to restrain HCV infection. Thus, immunoglobulin levels were still increased after three years on HAART. No differences in CD21 expression analysis were found between HIV-only infected patients and HCV-coinfected ones, suggesting that B cells were not activated by hepatitis C virus through CD21.

OP 7.5.

Liver Transplantation in Five HIV-infected Patients With Virus Hepatitis Induced Cirrhosis

Radecke K, Frühauf NR, Miller M, Ross B, Köditz R, Malago M, Treichel U, Broelsch CE, Gerken G. Department of Gastroenterology and Hepatology, Department of General Surgery and Transplantation, University Hospital Essen (Essen, Germany)

Introduction: Liver transplantation in HIV-infected patients with end-stage liver disease is under current debate. We report on our experiences with five HIV-infected patients, who underwent orthotopic cadaveric liver transplantation (OLT) at our transplantation center.

Methods: Between July 1998 and October 2001 five HIV-infected patients underwent OLT because of virus induced liver cirrhosis. One patient suffered from HBV-, three patients from HCV- and one patient from HCV/HBV/HDV-related cirrhosis. Mean duration of HIV infection was 15 years (range 12 - 17 years). Before OLT mean CD4 T-cell count was 299 cells/ μ l (range 86 - 621), mean viral load was 39926 copies/ml (range < 50 copies - 175000 copies/ml). Patients were prospectively followed-up with a mean duration of 25,6 months (range 3 - 61months).

Results: Three patients died three, ten and 31 months after OLT, respectively, due to graft failure. Causes of graft failure were: recurrent thrombosis of the hepatic artery, HCV-associated cholestatic hepatitis and chemotherapy-induced liver damage due to Hodgkin's disease, which was diagnosed 17 months after OLT, in addition to chronic HCV disease. In these patients intolerance of antiretroviral therapy after OLT was associated with HIV disease progression. The two survivors show a stable liver function and non-progredient HIV infection under antiretroviral therapy 61 and 23 months after OLT, respectively.

Discussion: A medium- or even long-term survival after OLT can be achieved in HIV-infected patients without progression of HIV disease under antiretroviral therapy. However, in our study three out of five patients died due to graft failure. Therefore, prognostic criteria have to be defined for the selection of HIV-infected patients, who may benefit from OLT.

OP 8.1. NF90ctv, a cellular dsRNA binding protein inhibits the Rev-dependent export of HIV-1 RNA

María Eugenia Castaño¹; Ajit Kumar² and Silvio Urcuqui-Inchima^{1*}

¹Immunovirology Laboratory, Faculty of Medicine, University of Antioquia, Medellín, Colombia

²Department of Biochemistry and Molecular Biology. The Georges Washington University, Medical Center, 23001 Street, NW, Washington, DC 20037. * To whom

correspondence should be addressed: surcuqui@virologia.udea.edu.co

Upon entering the uninfected host cell, the Human immunodeficiency virus type 1 (HIV-1) copies its single-stranded RNA genome into double-stranded DNA that is integrated into the host genome, at which step it is designated as provirus. The transcription of proviral DNA by host cell RNA polymerase II yields three types of viral transcripts: full spliced, singly spliced and unspliced transcripts. The spliced transcripts, are exported to the cytoplasm and translated as yielding the 'early' viral proteins, Tat, Rev and Nef. Among these, Rev possess the unique property of exporting unspliced and partially spliced viral transcripts that encode the structural viral proteins. The Rev-mediated nucleo-cytoplasmic transport of viral RNA is strictly dependent upon its interaction with RRE RNA structural element present in the target molecules. Since the Rev-RRE complex formation depends on RNA-protein interactions, we reasoned that ectopic expression of a dsRNA-binding protein might interfere with normal Rev-mediated transposrt of RNAs that encode viral structural proteins. The double-stranded RNA (dsRNA) binding nuclear protein 90 (NF90) has been suggested to function as transcription activator of the IL-2 gene by binding to the ARRE-2 sequence present in the promoter region. We studied the properties of a C-terminal variant of NF90 (NF90ctv), in stably transduced HIV-1 target cell line (GHOST/CD4+/CXCR4+ cells), and observed marked attenuation of viral replication (krasnoselskya-Riz et al., 2002). The in vitro studies reported here suggest a mechanism of inhibition of Rev-function and viral replication that may include NF90ctv-mediated interference of HIV-1 Rev based on protein-protein interactions that involve Rev binding to specific domains of NF90ctv.

OP 8.2.

Expression of HIV-1 gp160 in Transgenic Animals.

Dr. F. Berrada, Al Akhawayn University in Ifrane, School of Science & Engineering, Ifrane Morocco

The human immunodeficiency virus (HIV-1) is known for its ability to primarily infect lymphocytes T CD4+ as well as monocytes/macrophages. Productive infection has also been reported in brain tissue, gut epithelium and bone marrow cells. The infection with HIV-1 leads to a progressive degeneration of the immune system and a neurological dysfunction, termed AIDS dementia complex.

AIDS has been related to the striking loss of CD4+ T cells. However, the mechanisms underlying the neurological disorder are still not well understood. Previous in vitro studies have shown that the viral glycoprotein gp120 is toxic for cells of neuronal origin, which suggested that this toxic effect could possibly account for the ADC frequently observed in patients at their late stage of disease. Hence, we have constructed recombinant plasmids with the gp160 gene under the control of different heterologous promoters. We assessed the expression in vitro first, to test for the ability of those promoters to drive the expression of HIV-1 gp120 and later used the constructs to develop our transgenic mice. We analyzed different organs of the transgenic animals for the expression of gp160, at the RNA and protein levels, and examined different tissues for eventual harms. The methodology and results will be discussed during the presentation.

OP 8.3.**Polymorphisms in CCR5 promoter are associated with rare HIV-1 infection of the D32/D32 homozygous individuals**

Xihau Lu, Ghalib Alkhatib, R. Tubiana and L. Meyer

Indiana University School of Medicine, Indianapolis, Indiana, USA

Human CC chemokine receptor 5 (CCR5) is the coreceptor for macrophage-tropic (R5) HIV-1 isolates. Individuals lacking this coreceptor are highly protected against HIV-1 infection. The CCR5 gene in these individuals has been found to contain a 32-bp deletion that results in a frame-shift mutation and produces a truncated protein that cannot function as a coreceptor. In a recent study, we demonstrated that expression of CCR5D32 protein downmodulates the HIV coreceptor expression resulting in protection against HIV-1 infection (Agrawal et al., *Journal of Virology* 78 (5): 2277). Although the D32/D32 homozygous genotype is associated with protection against infection, some rare individuals with this genotype have been found seropositive for HIV-1. The mechanisms of HIV-1 infection of these individuals are unknown. To explore possible mechanisms, we analyzed six different infected individuals with the D32/D32 homozygous genotype. Our results demonstrate that the CCR5D32 protein encoded by the deleted CCR5 gene was detectable in all uninfected D32/D32 individuals examined and only one infected homozygous individual. However, the levels of CCR5D32 protein in that infected individual were severely reduced compared to those in uninfected D32/D32 individuals. The CCR5D32 protein was not detectable in five different infected D32/D32 individuals. The reasons for the absence of detectable protein varied from polymorphisms in their CCR5 promoter region, different patterns of transcription, or a point mutation in CCR5D32 ORF in one individual that resulted in an unstable protein. The effect of promoter polymorphisms was directly examined in a reporter gene activation assay system. Quantitation of the mRNA produced endogenously in PBMCs of the infected individuals correlated well with weak CCR5 promoter activity in vitro using individuals promoter constructs driving firefly luciferase gene. These results demonstrate that expression of CCR5D32 protein is critical for protection against HIV-1 infection in vivo.

OP 8.4.

Evaluation of porcine thymic xenografts to restore human thymopoiesis that is resistant to HIV infection

Sima Hadidi, Scott Damrauer, Ping Lan,

Yong-Guang Yang, Megan Sykes

Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Highly active antiretroviral therapy (HAART) has dramatically changed the prognosis of human immunodeficiency virus (HIV) infection. However, immune reconstitution, a critical component of recovery after treatment of HIV-1 infection, is not always achieved following HAART. We have previously demonstrated that porcine thymic xenografts support human thymopoiesis in immune deficient mice, and that the human T cells that develop in these grafts are specifically tolerant to the porcine thymus donors. We hypothesized that porcine thymic xenografts might provide an HIV resistant milieu for human immune reconstitution in the setting of HIV-1 infection. Human fetal liver tissue was grafted with human or porcine thymic tissues (Hu/Hu and Sw/Hu grafts, respectively) under the kidney capsule of NOD/SCID recipient mice that received 1.5 Gy total body irradiation. The grafted animals also received an intravenous injection of 1×10^4 CD34+ cells isolated from human fetal liver tissue. Recipient mice were then followed for human T lymphocytes in their peripheral blood, and at 10 weeks post-transplantation, those with human T cell reconstitution either received an intra-graft injection of 2000 TCID₅₀ of NL4.3 HIV strain or were mock-infected with supernatant from uninfected control PBMC culture. Mice from various experimental groups were sacrificed at 3 weeks post-infection, and different tissues including blood and grafts were harvested. Plasma viral RNA load, the size of the grafts and expression of mouse CD45 (Ly-5), porcine CD2 (MSA-4), human (h)CD3, hCD4, hCD8, AnnexinV, HIV antigen p24 and BCL-2 were assessed using appropriate techniques. Our results showed that the cellularity of NL4.3-infected Sw/Hu grafts was in the same range as that of mock infected human and swine grafts. In contrast, there was a marked loss of cellularity in NL4.3-infected Hu/Hu grafts. There was a significant decrease in the numbers of CD3+, CD4 single positive (SP) and CD8SP human T cells in the periphery and of double positive (DP) and double negative (DN) as well as CD3+, CD4SP, CD8SP human T cells in the grafted tissues of NL4.3-infected compared to mock-infected Hu/Hu recipient mice. In contrast, these numbers remained similar between NL4.3-infected Sw/Hu and mock-infected Sw/Hu or Hu/Hu recipients. Expression of p24 and AnnexinV was also markedly higher in the NL4.3-infected Hu/Hu compared to Sw/Hu recipients infected with NL4.3. In contrast to the levels of p24 and AnnexinV, the expression of BCL-2 was suppressed in various subsets of human thymocytes, especially DP and CD4SP T cells of NL4.3-infected Hu/Hu recipients, while it displayed a normal pattern of expression in all other recipient groups. The level of plasma viral RNA was comparable in both NL4.3-infected Hu/Hu and Sw/Hu recipients. These data suggest that swine thymic xenografts may permit immune reconstitution in patients with resistant T-tropic HIV infections by protecting human thymocytes from HIV-mediated destruction.

OP 8.5.**Pol mutations and polymorphisms associated with NRTI and NNRTI-based regimens in Botswana patients infected with HIV-1 C.**

Doualla-Bell F, Gaseitsiwe S, Ndung'u T, Modukanele M, Peter T, Novitsky V, Ndwapi N, Gaolathe T, Avalos A, Wester W, Bussmann H, Cardiello P, Marlink R, Moffat H, Thior I, Essex M, Wainberg MA. McGill AIDS Centre- McGill University (Montreal, Canada) Botswana-Harvard Partnership for HIV Research and Education (Gaborone, Botswana), Harvard School of Public Health (Boston, USA)

Background

HIV-1 subtype C (HIV-1C) is the predominant virus causing AIDS epidemic in Botswana, a country with an adult prevalence rate of HIV infection of approximately 35%. Nationwide introduction of HAART in Botswana in early 2002 necessitated characterization of pol polymorphisms and mutation patterns in the treated HIV-1C infection.

Methods

Twenty-two patients attending the Infectious Disease Care Clinic (IDCC) of Princess Marina Hospital between May 2001 and March 2003 were included in this study. Among the sixteen ARV-treated patients, 8 started HAART regimens containing ddI/d4T/NVP or EFV (arm A) while the 8 others started the CBV/NVP or EFV regimen (arm B), the first line regimen currently provided by the Botswana ARV national program. Longitudinal samples were sequenced for the region encompassing the entire HIV-1 protease and the first 335 amino acids of reverse transcriptase. Translated amino acid sequences were analyzed for the presence of polymorphisms and mutations associated with drug resistance.

Results

Although polymorphisms were found in both naïve and treated patients, many of them (K20R, K22N, E40D, V60I, I135T, I142V, K166R, K281R) were primarily observed in treated patients. Primary mutations associated to NNRTI and NRTI resistance were only observed in 10 out of the 16 treated patients. The V106M mutation, previously shown as associated with EFV resistance in HIV-1 C, was harbored by a patient treated with NVP. Appearance of the M184V mutation in the arm B patients (CBV/NVP or EFV) coincided with a slight rebound of viral load ($4.3 \pm 0.1 \log_{10}$ RNA copies/ml) and significantly improved immunologic parameter ($CD4 = 207.0 \pm 48.1$ cells/ μ l; $p < 0.05$). Interestingly, patients developing M184V mutation preferentially harbored polymorphisms Q174K and/or I178L located in the close proximity to the RT position 184. These patients also developed I135x polymorphism at the same time than M184V mutation.

Conclusion

The M184V mutation was associated with a clear clinical benefit at the time of its occurrence in 3TC-containing HAART. The co-existence of specific polymorphism in patients harboring M184V mutation associated with their localization in RT containing this primary mutation may warrant further studies including analysis of HIV-1C RT-specific T cell immune responses.

OP 8.6.

Aminoglycoside-arginine Conjugates: Chemical Barriers of HIV-1 entry

Aviva Lapidot and Gadi Borkow

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel

We have designed and synthesized aminoglycoside arginine conjugates (AACs) as anti HIV-1 agents (1-3). The most potent anti-HIV-1 AAC is the hexa-arginine neomycin B conjugate (NeoR6). AACs inhibit HIV-1 replication, including the binding/fusion step of the viral cycle. Although designed as Tat antagonists, they also compete with monoclonal antibody binding to CXCR4, and with SDF-1 and HIV-1 gp120 cellular uptake, strengthening the notion that they interfere with initial steps of HIV-1 infection. Part of this competition may be explained by the structural mimicking of the AACs and gp120. The core and the number of arginines attached to a specific aminoglycoside are important for their anti-HIV potency (3). NeoR6 resistant isolates have the following mutations in the surface glycoprotein gp120: I249T in the C3 region, S283L in the V4 region, and Q306L in the C4 region; and in the transmembrane glycoprotein gp41: S640R and F645Y in the 'heptad repeat' 2 (HR2) (4). This strongly suggest that NeoR6 obstruct HIV-1 replication by interfering with the fusion step, dependant of both conformational changes in gp120 following CD4 and CXCR4 interaction, as well as by conformational changes in gp41 induced by HR1 and HR2 interaction. One mutation in the gp120 C4 region associated with a change of nonpolar (Q) to polar (K) amino acid residues. Similarly, two positions in the HR2 of gp41 are associated with changes of nonpolar (S and F) to polar (R and Y) amino acid residues. Nonpolar residues appear to be important for the antiviral activity of NeoR6. The role of the V3 domain in the interaction of gp120 with CXCR4 has not been directly demonstrated; variable domains such as V1/V2 and V3 of gp120 can both contribute to the interaction with CXCR4 coreceptor. Therefore, mutations in NeoR6 resistant isolates may confer resistance by allowing the interaction of gp120 with CXCR4 in such a way that NeoR6 interference would be minimized. The mechanism of the dual functions of NeoR6, inhibiting HIV-1 entry by binding CXCR4 coreceptor and inhibiting the fusion process is being further investigated. The AACs may thus represent a novel family of fusion inhibitors. References: 1. Litovchick et al, *Biochemistry* 39:2838, 2000. 2. Litovchick et al, *Biochemistry* 40: 15612, 2001. 3. Borkow et al, *Antiviral Research* 60:181, 2003. 4. Borkow et al, *BBRC* 312:1047, 2003.

OP 8.7. Pharmacological Blockade Of Receptors Connecting To Inhibitory Pathways Of Immune Cells May Be An Efficient Immunopotentiating Treatment Of HIV/AIDS

Peuschel KE. Independent Researcher, Lugano, Switzerland

Introduction: HIV infection utilizes the inhibitory cAMP-PKA pathway of CD4 cells to enhance its own replication and simultaneously to downregulate the performance of the CD4 cell by shutting it down via upregulation of the cAMP-PKA pathway. It has been shown for example that Methamphetamine feeding the cAMP-PKA pathway upregulates HIV-replication 15-fold, therefore drugs blocking receptors feeding this pathway may be very efficient in blocking not only the replication of HIV but at the same time would enhance the general performance of the CD4 cell and could be an interesting additional approach in the treatment of HIV/AIDS. Two examples of receptors connected to the cAMP-PKA pathway in cells of the immune system will be presented including clinical observations confirming an enhanced performance of the immune system with pharmacological blockade of this pathway.

Methods: Theoretical review.

Results: Pharmacological blockade of receptors feeding the cAMP-PKA pathway can be used as an HIV/AIDS treatment downregulating HIV-replication and enhancing the performance of the immune system, especially of CD4 cells.

OP 8.8. Structure of Viral Antitermination Complexes

S. Schwarz, U. Scheckenhofer, S. Prasch, A. Eisenmann, K. Schweimer, B. Wöhl, & P. Rösch
Lehrstuhl für Biopolymere, Universität Bayreuth, 95440 Bayreuth, Germany

The HIV Tat/TAR system is supposed to work as an antitermination system, similar to the better known antitermination systems from phages lambda and HK022. Antitermination is a necessary step in HIV replication, and disruption of the antitermination complex consisting of Tat protein, TAR recognition RNA, human cyclin T1, and RNA Polymerase II would prevent viral proliferation. No drug, however, that specifically and efficiently targets the HIV antitermination complex is known so far. In order to progress towards the rational, structure based construction of inhibitors of the formation of the HIV antitermination complex it would be highly desirable to obtain information on the three-dimensional structure of this complex. Although the tertiary structures of several peptid-RNA complexes involved in viral antitermination have been determined in recent years, the HIV antitermination complex itself has eluded all efforts to this end.

In addition to the HIV system, we study the bacteriophage lambda antitermination factor, N protein, and its RNA and protein complexes in a more general approach towards the understanding of the mechanisms involved in antitermination processes. N protein prevents termination of transcription by *E. coli* RNA polymerase at rho-dependent and independent terminators in the lambda early operons. The modifications of the RNA polymerase by the N protein requires the nutboxB hairpin of N utilization sites (nut) and the *E. coli* factors NusA, NusB, NusG, and NusE to form the stable and processive antitermination complex. As HIV Tat, N protein contains an arginine-rich RNA binding motif (ARM) at the NH₂-terminus responsible for specific recognition of nutboxB-RNA (boxB). NMR and CD experiments indicate that free N protein is unstructured in solution and becomes partially structured only upon binding to boxB. The NH₂-terminal peptide N(1-36) is sufficient to ensure boxB binding, and all structural changes in N protein that occur upon binding to boxB are localized within this peptide. The COOH-terminal region is required for binding to NusA and the RNA polymerase. Nun protein from coliphage HK022 binds to boxB RNA as well but, in contrast to N protein, functions as a transcriptional terminator.

We expressed and isotopically labeled several proteins and protein domains of the antitermination complexes of HIV, phage lambda, and phage HK022 (e.g., N, Nun, RNA-Polymerase, NusA, Tat, cycT1) and, for the latter two system, could directly show by NMR-titrations that the interaction sites between the various proteins are highly modular, and their interaction domains are basically independent of the rest of the proteins. We were able to determine large parts of the structure of these antitermination complexes by NMR and molecular dynamics calculations.

OP 8.9.**The VirtualPhenotype™ Analysis of an HIV-1 Genotype Provides a More Accurate Prediction of Drug Susceptibility Than a Single Phenotype Measurement**

Van Houtte M, Vermeiren H, Lecocq P, Winters B, Pattery T, Mc Kenna P, Bacheler L. Virco BVBA, Mechelen, Belgium; VircoLab Inc, Durham, NC, USA

INTRODUCTION: VirtualPhenotype™ provides a quantitative prediction of antiretroviral drug resistance based on a database of viral genotypes and corresponding phenotypes for >32,000 clinical isolates. When a genotype is analyzed, drug-specific patterns of resistance-associated mutations are identified and isolates with similar patterns of mutations are selected from the database. The matching phenotypes of these isolates are averaged to provide a prediction of fold-change (FC) in IC_{50} relative to a reference wild-type. Here we assess the contribution of phenotype assay variability to observed differences between predicted and measured values.

METHODS: VirtualPhenotype™ analysis was performed on a panel of 7 clinical isolates with a broad range of drug-resistance levels. The panel was repeatedly tested over a period of two years for phenotype against 16 antiretroviral drugs, comprising a total of 733 measurements. The contribution of phenotype assay variability to observed differences between predicted and measured values was assessed by analysis of variance. FC, mean FC, and 95% confidence intervals were calculated for each drug for 1) individual phenotype test results, 2) the mean of replicate phenotype test results, and 3) VirtualPhenotype™ predictions.

RESULTS: The root mean square error (RMSE), an estimator of the standard deviation of the difference between measured and predicted phenotype, averaged 0.35 logFC (range: 0.27, lamivudine to 0.60, delavirdine). Phenotype assay variability was the major contributor to differences between measured and predicted FC values, accounting, on average, for 81% of RMSE. FC values predicted by VirtualPhenotype™ analysis corresponded very closely ($r^2=0.93$, $p<<0.0001$) to the mean of replicate phenotype measurements. For this panel of isolates, the number of matching geno-phenotypes available for predicting FC values ranged from 25 to 14318 (median = 325). Consequently, the confidence intervals for the predicted FC values were very small compared to those for individual or multiple replicate phenotype tests.

CONCLUSIONS: VirtualPhenotype™ analysis of HIV-1 genotype provides a precise, quantitative prediction of drug susceptibility phenotype. By averaging results across multiple isolates with similar mutational patterns, VirtualPhenotype™ overcomes the variability inherent in any biological assay and provides a prediction of drug susceptibility phenotype that is more precise than an individual phenotype measurement.

OP 9.1.

Chinese SARS and AIDS Control at Frontier Ports

Song Mingchang, Lu Yonggui, He Yuping

No.9, Madiandonglu Haidian District Beijing 100088 P.R..CHINA

1. In last year, we have being taken Eight Measures and Five "None missed" fight SARS at frontier ports.

1.1 Eight Measures:

Health declaration;

Temperature check;

Medical tour of inspection;

Patient deportation;

Disinfection and ventilation;

Report Real-time epidemic information;

Self-protection;

Propaganda and education;

1.2 Five "None missed":

Fill in health declaration card without any one missed

Check temperature without any one missed .

Any one who has high fever (>38?)is sent to hospital without any one missed.

Every day report the SARS quarantine information without any one missed.

Every health declaration card is kept well without any one missed.

1.3 Effect of eight measures and Five "None missed" :

From April to July, 40.6 million entry-exit people had been checked by infrared temperature instrument;

33.5 million health declaration cards were checked;

15404 people were found to have some symptoms like SARS;

Five case were diagnosed as SARS;

No SARS case transmitted abroad through frontier ports;

No quarantine staff was infected by SARS;

2. From 1985 to 2003, 8.9million entry-exit people had been guarded past.1991 people with living HIV had been detected.

OP 9.2.

HIV-1 subtypes in the Northern Border Region of Kenya

Lihana RW, Lwembe RM, Kiptoo MK, Ochieng W, Oishi I, Ichimura H, Songok EM. Kenya Medical Research Institute, Jomo Kenyatta University of Technology, KEMRI/JICA Project, Nairobi, Kenya

Background: Most molecular epidemiological studies of HIV in Kenya have been done in the central, western and coastal regions and areas bordering Uganda and Tanzania. In these regions, subtype A1 has been found to be dominant. No information exists about the situation of HIV-1 in northern Kenya, especially areas bordering Ethiopia, Sudan and Somalia. This study was carried out to determine the distribution of HIV-1 env subtypes along the northern Kenya border region.

Methods: One hundred and fifty two (152) HIV-1 antibody positive samples were collected from blood transfusion centres and STD clinics in Moyale, Kakuma, Mandera and Lokichogio. Proviral DNA was extracted and amplified using primers designed from a highly conserved region of group M and O sequences of gp41. Fragments of about 460bp spanning approximately 40 % of the gp41 region were amplified and sequenced directly. Sixty-two (62) of these samples were successfully analyzed and classified into HIV-1 subtypes by sequence-based phylogenetic analysis.

Results: Results of this analysis show that the following subtypes of HIV-1 are circulating in this region: Subtype C: 26 (42%); Subtype A1: 27 (43%) and Subtype D: 9 (15%).

Conclusions: Unlike other parts of Kenya where subtype A1 is dominant, the northern border region of Kenya has subtypes A1 and C in circulation in equal proportions.

OP 9.3.

Method of Treatment of Acquired Immune Deficiency Syndrome with Embryonic Hematopoietic Stem Cells

Smikodub OI. Cell Therapy Clinic of National Medical University and Embryonic Tissues Center EmCell, Kiev, Ukraine

This method is protected by two US patents: ? 5,811,089 from Sep. 22, 1998 and # US 6,184,033 B1 from Feb.6, 2001, Dutch patent # 194908 from Sep.15, 2003, and Russian patent #2137484 from Sep.20, 1999. It allows for stabilization and restoration of functional activity of the immune system and compensation of insufficient immune response of the patient with simultaneous decrease of clinical manifestations of the disease

The main group consisted of 48 patients for whom preliminary selection criteria have been developed: impossibility of antiviral therapy due to intolerance or considerable side effects; more than 50% decrease in CD4+ during preceding 6 months or reduction by 100/1 mm³ during the same time; disease progression: transition from HIV to AIDS-AC, and from AIDS-AC into AIDS despite anti-virus therapy; impaired workability and quality of life (decrease in Karnofsky index by more than 20% during last 6 months); CD4+ count less than 50/mm³ with manifestations of AIDS-indicator diseases, and with Karnofsky index below 30%

Developed is an original cell composition containing embryonic hematopoietic stem cells. Its application led to increase of immune indices including CD4, CD3, CD8 subpopulations; the most demonstrative was this increase in the group of patients with CD4+ count 200-300 mm³: at the end of the first post-transplant week, it rose by 35%, second week - by 72%, and in 1 and 6 months it was higher by respectively 51% and 42%. High levels of lymphocytes were maintained in patients in 3-6 and even in 10-12 months after transplantation. Reported were also normalization of peripheral blood count (leukocytes, erythrocytes, thrombocytes), decrease in infectious complications and manifestations of peripheral neuropathy and related neurological symptoms, disappearance of astheno-neurotic syndrome, optimization of psychoemotional state with decrease of depression signs, improvement of mental and physical activity, weight gain, and substantial inhibition of the progression of the disease.

OP 9.4.

Andrieu unjustly disregarded. Better CD4-counts with Prednisolone

Ulmer, Albrecht; Mueller, Markus; Frietsch, Bernhard

HIV-Practice, Schwabstr. 26, Stuttgart D-70197, Germany

Background: In 1995 J.M. Andrieu (Paris) reported a CD4 increase with prednisolone in asymptomatic HIV patients. In the following years this was disregarded. Admittedly he used relatively high dosages, but the principle proved to be interesting: For a few years now we have noticed that the small dose of 5 mg Prednisolone, which can be used nearly without side effects for many years, has similar effects.

Methods: 60 therapy naïve patients with a CD4 count of at least 300/μl (mean 563) were treated for 0,5 - >11,5 years with prednisolone (5mg daily). CD4 profiles and viral load were compared retrospectively and ongoing with those of all untreated control patients (n = 133, mean CD4 612/μl). 128 patients received the same dosage of prednisolone >6 months during therapy interruptions (STI), 85 of them from the STI outset. They were compared with those receiving no prednisolone in their first 6 STI months (n = 41). Also the CD4-development of all patients with prednisolone during STI for >1 year, meanly 681 days, was documented (n = 99).

Results: A CD4 increase was observed in therapy naïve patients with prednisolone (after 3 years +127/μl), a decrease in the patients without prednisolone (after 3 years - 193/μl, p=0,0016). The same was observed in relative counts and CD4-/CD8-ratio. No significant difference, but also a trend in favour of prednisolone was determined in the development of the viral load. During STIs the CD4 decrease was more flat with prednisolone (0,46 instead of 0,77/die, p=0,0157). In 29 out of 39 (CD4) matched pairs the patients with prednisolone showed better CD4-development. Meanly all patients with prednisolone of the matched pairs lost 0,25 fewer CD4 cells/d. The mean CD4 count of the 99 STI patients taking prednisolone for >1 year sank from 672/μl to 524/μl. So STI could still be considerably increased in the majority.

Conclusions: It seems possible to reach a notable prolongation of time without HAART by means of low-dose glucocorticoid therapy. This could be of importance when considering costs and side-effects of HAART.

OP 9.5.

Enhanced Immunogenicity of HIV-1 Whole Killed Vaccine in Association with Amplivax™

Trabattoni D, Clivio A, Gori A, Bartholomew R, Fernandez-Cruz E, Lowry P, Kandimalla ER, Sullivan T, Bhagat L, Agrawal S, Clerici M, TheofanG, Bray DH. Dept Immunol, Dept Biol, Milano University, Dept Infect Dis, Milano, Italy; MRC Clinical Trials Unit, London, UK; Gregorio Maraon Univ Hospital, Madrid, Spain; Hybridon, Inc, Cambridge, Immune Response Co, Carlsbad, USA

The immunogenicity of HIV-1 Immunogen combined with Amplivax™, a second-generation immunomodulatory oligonucleotide, was examined in two different model systems. HIV-1 Immunogen, also known as REMUNE®, is a gp120- depleted HIV-1 antigen emulsified in Incomplete Freund's Adjuvant (IFA). In the first model, C57/BL6 mice immunized subcutaneously with a combination of HIV-1 Immunogen and Amplivax™ showed significantly enhanced HIV-specific production of p24 antibody, HIV-specific IFN- γ (both quantity and number of CD4 and CD8 T cells producing it), chemokines (RANTES, MIP-1 α , MIP-1 β), and IL-10 when compared to HIV-1 Immunogen or Amplivax™ alone. Importantly, the enhancements by Amplivax™ were still observed if HIV-1 antigen was not emulsified with IFA. In the second model, Amplivax™ was investigated ex-vivo for its ability to enhance HIV antigen stimulation of PBMC isolated from HIV+ patients treated with antiretroviral therapy (ART). Patients were either non-immunized, or previously immunized with HIV-1 Immunogen. Both patient groups had comparable CD4 counts, HIV plasma viremia, duration of infection, and ART. showed that Amplivax™ induced stronger HIV-specific cell-mediated immune responses in patients vaccinated with HIV-1 Immunogen, as measured by total spots produced in the IFN- γ ELISPOT assay and a higher percentage of alpha defensin-producing cells. Both effects were most evident using 1 μ g/ml of Amplivax™.

Preliminary data from an ongoing clinical trial in drug-naïve HIV+ patients suggest that HIV-1 Immunogen also has a positive effect on generation of HIV-specific immune responses in this patient population. The potential enhancing effect of Amplivax™ will be tested later this year in these patients that will have Amplivax™ added to the HIV-1 Immunogen as part of the vaccine.

OP 9.6.**ESAT-6 and CFP-10 derived peptides for diagnosis of TB infection in severely immunocompromized HIV-infected individuals**

Fortis C, Tasca S, Mantegani P, Lazzarin A, Scarpellini P. IRCCS San Raffaele, Milano, Italy

HIV infection is considered the strongest risk factor for the development of tuberculosis (TB). The tuberculin skin test (TST), using PPD, is largely utilized for both diagnosis and screening. However, the broad antigenic cross-reactivity of PPD with antigens derived from several mycobacterial species causes the poor specificity of TST. Moreover, up to 50% of TB patients coinfectd with HIV have a negative TST. M tuberculosis infection evokes a strong cell-mediated immune response, and detection of specific T cells might be a means to detect infection. We selected and pooled 5 highly immuno-genic and largely HLA-DR-restricted peptides of 20 aa in length, 3 deri-ved from ESAT-6 and 2 from CFP-10, two secretory proteins highly specific of M tuberculosis, and used as antigens in an ELISPOT-IFN- γ assay and compared with the responses to PPD and BCG antigens. 27 HIV-infected, severely immunocompromized individuals, and 41 HIV negative subjects were enrolled and classified for TB infection following directions of the American Thoracic Society. 9 HIV+ and 20 HIV-subjects were classified as 3 or 4 (active or previous TB). The ELISPOT-IFN- γ assay resulted high specific (87.5%) and sensitive (93.1%) for detection of M tuberculosis infection. 3 out of 18 (16.7%) class 0 (TST neg), but HIV-infected individuals responded to peptides. Conversely, 2 out of 9 (22.2%) HIV+ patients with active TB, both TST neg, did not respond to peptides. One had an immune reconstitution syndrome cha-racterized by a very high spontaneous activation of their lymphocytes able to mask any response to antigens or peptides. Of note, all the HIV+ patients that responded to peptides also responded to BCG, and all that where neg to BCG were also neg to peptides, while 8 out of 18 BCG pos did not respond to pepti-des (previously vaccinated or infected with mycobacteria other than tuberculo-sis; MOTT). The mean number of spot forming cells x million PBMC in response to peptides was significantly higher in TB class 3-4 subjects vs class 0 (but significantly lower in HIV+ respect to HIV- subjects; $p=0.022$). While no significant differences were observed between HIV+ and HIV- TB class 0 individuals. In conclusion, the pool of peptides resulted to be very specific and sensitive for diagnosis of TB infection, and able to discriminate between BCG-vaccinated or MOTT-infected individuals and TB infected individuals. Moreover, the test allowed to recognize TB infected individuals also in some severely immunocompromized, HIV+ subjects otherwise recognizable.

OP 9.7.

Why the patient's perspective is critical in the management of lipodystrophy?

Duracinsky M1, Cervoni J2, Bourgarit A3, Sereni D3, Molina JM3, Wu A4, Chassany O3.

1Hopital de Bicêtre; 2Hopital Lariboisiere, 3Hopital Saint-Louis, Paris, France; 4Johns Hopkins University, Baltimore, USA.

Background: Lipodystrophy may greatly impairs quality of life (QoL). Nevertheless, the recognition of the scientific value of QoL and more broadly the patient's perspective in evaluating therapies is questioned. It may be useful to quantify the added value of the patient's perspective, using correlations between patient-reported outcomes (PROs) and clinician-reported and biological outcomes.

Methods: We performed a cross-sectional survey in 143 HIV French outpatients with lipodystrophy. Clinical and demographic data were collected. Patients completed a new specific lipodystrophy questionnaire "Assessment of Body Change and Distress" (ABCD), consisting of 3 parts: signs of lipodystrophy (6 items), global satisfaction (n=1) and 20 items evaluating QoL. A HIV specific (MOS-HIV) and generic (SF-12) QoL questionnaires were also filled-in.

Results: Mean age was 43 ± 10 yrs (71% of men), and mean duration of HAART was 4.5 ± 1.7 yrs. ABCD QoL score is weakly or no associated with viral load ($r=0.03$), CD4 count ($r = 0.13$) and CDC classification ($p = \text{NS}$). Its correlation with the clinician's report of number of sites of lipodystrophy is weak ($r = 0.17$). Correlations between different PROs are logically higher. ABCD QoL score is more correlated with the patient's report of number of sites of lipodystrophy ($r = 0.39$) and with satisfaction ($r = 0.58$). ABCD QoL score is correlated with health distress and social dimensions of the MOS-HIV ($r > 0.6$) and with mental component of the SF-12 ($r = 0.65$), but not with physical dimensions of these questionnaires ($r < 0.2$).

Conclusion: PROs are weakly correlated with biological markers, and although overlapping, each one of PROs measures a distinct concept. Clinicians cannot infer the QoL of their patients neither from a viral load nor from a clinical exam. The patient's perspective is essential in medical decision making and so it is with lipodystrophy.

OP 9.8.**A Technological Monitoring and Management-Support System for Anti-Retroviral Therapy in South Africa: Introducing Cell-Life**

S. Anand, U. Rivett, Cell-Life, University of Cape Town, South Africa

The last ten years of democracy in South Africa have been characterised by developments to build a new nation. Basic amenities such as water, sanitation and electricity have been delivered to the majority of the population, and the housing backlog is being addressed. Developments are now being challenged through the impact of HIV/AIDS. Sub-Saharan Africa has an estimated 28.1 million HIV infections. Within this region, South Africa is faced with one of the most severe HIV/AIDS epidemics in the world, with estimates of infections ranging between 4 and 6 million. The South African Government's anti-retroviral (ARV) operational plan came into effect in November 2003, with early 2005 estimated for the ARV roll-out. The provision and distribution of medication is however a logistical problem, requiring a structure for correct delivery of treatment. South African research has shown that support of the HIV+ individual through home based care systems ensures a higher level of adherence. It has also been shown that accurate data about the individual, the medical history, the socio-economic status of the family and the individual's diet have a major impact on the success of adherence to ARV treatment. The collection of such data has until now been a major challenge. The non-governmental organisation (NGO) Cell-Life has developed a system that offers a 'bottom-up approach', whereby the home-based carer captures information via a user-friendly mobile phone (cellphone) application. South Africa has one of the highest uptakes and demographic distributions of cellular technology in the world. With this infrastructure and technology at hand, Cell-Life implemented an innovative information-gathering and provision system, which uses relatively simple and accessible, available technology to manage the treatment of HIV/AIDS in South Africa and the continent. Cellphone enabled Wireless Internet Gateway (WIG) applications which use Global System for Mobile Communications (GSM) networks, easy-to-use database applications on the Internet, an HIV/AIDS database, and a Geographical Information System (GIS) have resulted in an overall HIV/AIDS Information Management System. The system has been in use since August 2002 at pilot sites, and is presently being introduced in several trial ARV programmes. An independent study on the effectiveness of the system has shown that it improves the data recovery and treatment management over conventional systems; and with further enhancements it will form a solid foundation for the nationwide ARV rollout.

OP 10.1.
SARS: past, present, future
No abstract available

OP 10.2. Clinical Management of patients with SARS

Joe Sung

Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

Severe acute respiratory syndrome (SARS) is a newly emerged infectious disease in the 21st century which has posed an enormous threat to international health. During the global outbreak in 2003, the most severely affected countries were China (Mainland China, Hong Kong, Taiwan, Vietnam, Canada, and Singapore). As of 31st July 2003, 8098 probable cases were reported in 29 countries and regions with a death toll of 774 (9.6%).

Due to limited knowledge of this newly emerged disease, treatment of SARS was empiric during the outbreak in 2003. Apart from supportive care, the appropriate treatment for different clinical stages of SARS is unknown at present. No prospective randomized, placebo-controlled study of any intervention has been reported. Respiratory failure is the major complication of SARS. Hypoxemia develops in approximately 50% of affected adults, 20-36% may require ICU admission whereas 13-26% may progress into acute respiratory distress syndrome (ARDS) necessitating invasive ventilatory support. Anecdotal reports have indicated that NPPV was effective in SARS patients with respiratory failure.

Ribavirin was empirically used in the treatment of SARS last year. After 2 weeks of ribavirin treatment, a substantial proportion of patients experienced a fall in hemoglobin of more than 2 g/dL from baseline. The use of ribavirin for SARS in Toronto, based on a higher dosage for treating haemorrhagic fever virus, was associated with more toxicity, including elevated transaminases and bradycardia. Nevertheless, ribavirin has no significant in-vitro activity against SARS CoV. Genomic analysis of the SARS-CoV has revealed several types of enzymatic targets including the proteases. In vitro anti-viral activity against SARS-CoV was demonstrated using a combination of lopinavir and ribavirin. Initial clinical studies suggested that this combination can reduce the requirement for ventilation and mortality of patients. Intravenous high-dose methyl-prednisolone (MP) has been given to prevent immunopathological lung injury, on the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response. The use of high-dose pulse MP during clinical progression was associated with more favourable clinical improvement with resolution of fever and lung opacities within 2 weeks. Interferon has been found to have the best anti-viral activity against SARS-CoV. In uncontrolled study in Toronto, use of IFN alfacon-1 plus corticosteroids was associated with reduced disease-associated impaired oxygen saturation, more rapid resolution of radiographic lung opacities and lower levels of CPK. In in vitro study, complete inhibition of cytopathic effects of SARS CoV in culture was observed for interferon subtypes, β -1b, ω -n1, ω -n3, and human leukocyte IFN- ω . In experimentally infected macaques, prophylactic treatment of SARS CoV infected macaques with the antiviral agent pegylated IFN- ω significantly reduces viral replication and excretion, viral antigen expression by type 1 pneumocytes and pulmonary damage, compared with untreated macaques, whereas post-exposure treatment with pegylated IFN- ω yielded intermediate results. These findings support clinical testing of approved IFN's for the treatment of SARS.

OP 10.3.

The SARS-CoV S glycoprotein as entry mediator, vaccine immunogen and target for inhibitors

Xiaodong Xiao, Samitabh Chakraborti, Yang Feng, Prabakaran Ponraj, Vidita Choudhry, You-qiang Wu, Mei-Yun Zhang and Dimitar S. Dimitrov

LECB, NCI-Frederick, NIH, Frederick, MD 21702, USA

Ph: 301-846-1352

Fax: 301-846-5598

Email: dimitrov@ncifcrf.gov

We have cloned, expressed and characterized the full-length, and various soluble fragments of the SARS-CoV (Tor2 isolate) S glycoprotein (Xiao et al., BBRC, 2003, 312: 1159, Dimitrov, Cell, 2003, 115, 652). Cells expressing S fused with receptor-expressing cells at neutral pH suggesting that the recombinant glycoprotein is functional, its membrane fusogenic activity does not require other viral proteins, and that low pH is not required for triggering membrane fusion; fusion was not observed at low receptor concentrations. S and its soluble ectodomain, Se, were not cleaved to any significant degree. They ran at about 180-200 kDa in SDS gels suggesting posttranslational modifications as predicted by previous computer analysis and observed for other coronaviruses. Fragments containing the N-terminal amino acid residues 17 to 537 and 318 to 517 but not 17 to 276 bound specifically to Vero E6 cells and purified soluble receptor, ACE2. A model was developed for the binding of these fragments to ACE2 (Ponraj et al., BBRC, 2004, 314: 235). By screening phage libraries we identified human antibodies that are potent inhibitors of the SARS-CoV entry and bind the S glycoprotein. These and other results that may help in the elucidation of the mechanisms of SARS-CoV entry, and in the development of vaccine immunogens and entry inhibitors, will be discussed (Dimitrov, Nat Rev Microbiology, 2004, 2:109).

OP 10.4. Multi-allelic detection of the Severe Acute Respiratory Syndrome-associated Coronavirus using 'sloppy' molecular beacons: A “molecular shotgun” approach of recognizing a moving target

Leondios G. Kostrikis

Department of Biological Sciences, University of Cyprus, 75 Kallipoleos Avenue, P.O.Box 20537, CY-1678, Nicosia, Cyprus

Background

Severe acute respiratory syndrome (SARS) is a recent emerging infectious disease first identified in Guangdong Province, China and later spread around the world including Canada. The causative agent of SARS is a new and phylogenetically distinct coronavirus strain, designated SARS-CoV, belonging in the single-stranded RNA Coronaviridae family. Recent molecular epidemiological studies have shown that SARS-CoV mutates at significant rate underlining the importance of improved diagnostic methodologies for monitoring the evolving SARS-CoV in human populations and preventing future outbreaks.

Material and Methods

The objective of this study was to develop and evaluate a novel diagnostic methodology for identifying evolving SARS-CoV quasispecies in clinical samples. The technology is based on real-time reverse transcriptase polymerase chain reaction using molecular beacons targeting multiple allelic sequences of SARS-CoV genome. Molecular beacons are stable hairpin-loop oligonucleotide probes that have sequence complementary to the target sequence of interest, and have a fluorophore and quencher at each end. When a probe is not bound to the target sequence, the fluorescence is quenched, but when bound to the target sequence the fluorescence is restored. 'Sloppy' molecular beacons have longer target recognition sequences in the loop that can tolerate several single base-pair polymorphisms without losing their fluorogenic properties.

Results

By using a multiplex real-time PCR and a combination of 'sloppy' molecular beacons with the same fluorophore and specific for four SARS-CoV genes (S, E, M, and N) we have been able to develop a SARS-CoV diagnostic assay that can tolerate about 10 percent diversity from the original Tor2 and Urbani strains. To evaluate the multi-allelic SARS-CoV assay, we analysed 60 clinical specimens obtained of patients who died of SARS during the recent epidemic in Toronto and 60 control specimens with sensitivity and specificity of 100 percent.

Conclusion

Our findings show that our new SARS-CoV diagnostic assay will provide a rapid and accurate method for monitoring the evolving SARS-CoV in human populations and prevent future outbreaks caused by genetically different strains.

OP 10.5.

Concentration and Detection of SARS Coronavirus in Sewage from Xiao Tang Shan Hospital and the 309th Hospital of the Chinese PLA

Junwen Li¹, Xin Wei Wang¹, Fu Huan Chao¹, Jinsong Li², Bei Zhen², Qingxin Kong¹, Nong Song¹, Min Jin¹, Wenjun Xiao², Changqing Gu¹, Jing Yin¹, Wei Wei²

¹. Institute of Hygiene and Environmental Medicine, Academy of Military Medical Sciences, 1 Da Li Road, Tianjin, 300050, P.R. China; ². Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences, 172 Dong Da Jie street, Feng Tai, Beijing, 100072, P.R. China.

A worldwide outbreak of severe acute respiratory syndrome (SARS) had been reported. Over 8439 SARS cases and 812 SARS-related deaths were reported to WHO from 32 countries around the world up till 5 July 2003. The mechanism of transmission of SARS-CoV has been limited to only close contacts with patients. On 15 April 2003, health authorities reported a total of 321 individuals affected by SARS who were residents in Amoy Gardens. The attention was focused on possible transmission via the sewage system because the laboratory studies showed that patients with the disease excreted coronaviruses in their stools. Since the positive RT-PCR results were obtained from stools of SARS patients, it hints that the stool of SARS patients or the sewage containing the stool of patients would transmit SARS-CoV. We used a novel style of electropositive filter media particle to concentrate the SARS-CoV from the sewage of two hospitals receiving SARS patients in Beijing, as well as cell culture, RT-PCR and sequencing of gene to detect and identify the viruses from sewage. There was no alive SARS-CoV detected in the sewage in this assays. The nucleic acid of SARS-CoV had been found in the sewage before disinfection from both hospitals by semi-nested PCR. After disinfection, SARS-CoV RNA could only be detected from the samples on June 11, 13 and 15 from the 309th Hospital. It is interesting that the RNA of SARS-CoV could be detected in the samples from the 309th Hospital, but not from Xiao Tang Shan Hospital after disinfection. It's found that there were two serious patients had been moved to other hospitals in Beijing on June 2 and 9, respectively before the experimental period. It was reported that the RNA of SARS-CoV could be survived for five days or much longer time[28]. In this study, it is found that the RNA can be detected in sewage for 8 days though the virus had been inactivation. In conclusion, this study demonstrated that there was no alive SARS-CoV in the sewage of both hospitals receiving SARS patients, but the RNA of SARS-CoV could be detected from the concentrates of sewage before disinfection and occasionally after disinfection. It provides strong evidence that SARS-CoV can be excreted through the stool/urine of patients into sewage system, thus the sewage system is a possible transmission way.

OP 10.6.**Purification, Characterization, and Immunogenicity of a Truncated Form of the SARS Spike Protein: Toward a recombinant glycoprotein subunit vaccine**

Kan E, Coates S, Stadler K, Matsuoka K, Calderon E, Song H, Seo MY, Wininger M, Barnett S, Ulmer J, Rappuoli R, Abrignani S, Houghto, M, Han J, Srivasta I. Chiron Corporation (Emeryville, USA); IRIS, Chiron S.r.l. (Siena, Italy)

The pandemic potential and pathogenicity of SARS-CoV, as well as the absence of effective licensed drugs, highlights the need for aggressive efforts toward the development of an effective SARS vaccine. Preliminary data indicate that a human monoclonal antibody directed toward the Spike (S) envelope glycoprotein of SARS-CoV (S3.2) neutralizes SARS-CoV in vitro and also protects mice upon challenge. Our strategy is to evaluate the potential efficacy of inactivated virus and recombinant protein vaccines for their ability to induce protective neutralizing antibody responses. Since spike protein is the main target for inducing antibody responses, we cloned both full length (nS) and truncated version of the spike (nS Δ TC) in an expression vector, and performed initial characterization of the expressed proteins. We have used bulk transfection methodology for producing smaller amount of nS Δ TC for further structural characterization and immunogenicity studies. Using optimized protocols, we were able to purify mg quantities of the nS Δ TC to near homogeneity. The purified protein is recognized by the MAb S3.2 and also by neutralizing anti-SARS rabbit sera indicating that neutralizing epitope recognized by S3.2 MAb is preserved and exposed in truncated spike protein. The molecular mass for the nS TC using SALDI system was found to be 178 kDa. We have immunized a group of ten mice with 3ug of the purified nS Δ TC protein intramuscularly at 0, 4, and 8 weeks intervals. The sera were collected 2 weeks after each immunization and analyzed for total binding and neutralizing antibody responses induced in these animals. All the animals induced high levels of specific antibody responses, which were comparable or better to those induced by inactivated SARS-CoV in mice. Moreover, these antibodies also neutralized SARS-CoV in an in vitro neutralization assay at significant dilutions. Our data indicate that neutralizing antibody titers induced by the recombinant proteins are comparable to the neutralizing titers induced by the SARS inactivated virus. We are currently evaluating the avidity and isotypes of these antibodies. These preliminary data demonstrate the strong potential for an effective recombinant protein vaccine against SARS.

OP 11.1.
AIDS in Africa: a terrible injustice

No abstract available

OP 11.2.**Has HIV Prevention some Efficacy in the Developed World?**

No abstract available

OP 11.3.
HIV no longer a Disease Apart?

No abstract available

OP 11.4. **Economic Threats on Fundamental Research**

No abstract available

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PP 1.1.

Trends in the HIV/Aids Epidemic in Women in the City of São Paulo, 1985 - 2000

Tancredi MV, Waldman EA. Referral and Training Centers for STD/Aids - São Paulo , Sao Paulo, Brazil

Background: The participation of women in HIV/Aids Epidemic occurred later and in a less expressive way than in men, but it increased faster in Brazil as in many others countries. This is an ecological study describing temporal trends of HIV/Aids in the City of São Paulo, from 1985 to 2000.

Methods: The objective was to analyze trends in incidence and mortality by Aids, in the city of São Paulo, in women older than 13 years, from 1985 to 2000, by age and exposure category. Study performed with data from new cases of Aids and deaths, reported to Epidemiological Surveillance of São Paulo State Program on STD/AIDS. Trends in 10,113 cases of Aids, with 5,204 deaths, were estimated using polynomial regression models, with a confidence intervals = 95% and the softwares EPI-INFO 6.04d and STATA 6.0.

Results:. Second order models were the best adjusted for trends in female incidence ($\text{LnY} = 6,82 + 0,25X - 0,04X^2$ with $r^2=0,98$ and $p<0,001$), incidence in heterosexual females ($\text{LnY} = 6,09 + 0,28X - 0,03X^2$ with $r^2=0,99$ and $p<0,001$) and for female IDU category ($\text{LnY} = 5,46 + 0,13X - 0,05X^2$ with $r^2=0,90$ and $p<0,001$). The best models for mortality trends, of all women, were also of second order ($\text{LnY} = 6,38 + 0,17X - 0,04X^2$ with $r^2=0,97$ and $p<0,001$), for heterosexual females ($\text{LnY} = 5,70 + 0,15X - 0,05X^2$ with $r^2=0,97$ and $p<0,001$) and for IDU females ($\text{LnY} = 5,14 + 0,05X - 0,06X^2$ with $r^2=0,93$ and $p<0,001$).

Conclusions: Trends in incidence among heterosexual female, of all ages, grew until 1997 decreasing thereafter. The same was observed in IDU women; witch increased till 1992 and became decreasing after this. The female mortality, witch attacks women during fertile period of life, increased until 1995 in all age groups. Changes in male / female rates, which decline from 28:1 in 1985 to 2:1 in 2000, pointed toward an expressive growth in the role of the heterosexual and female epidemic.

PP 1.2.

Les Jeunes Parlent aux Jeunes

Diatta A, Ndiaye MA, FALL MF. Groupe Communication Internationale en Technologie Cultures et Services en Afrique (G.CITCS Afrique), Dakar, Senegal

A l'heure des TIC et l'Internet principaux supports de développement du 3^e millénaire, le G.CITCS Afrique associe la sensibilisation à la formation pour la prise en charge des jeunes séropositifs, issus en général du milieu défavorisé de la banlieue de Dakar. Durant nos sessions de formation appelées "vacances numériques", nous référons les jeunes de plus de 20 ans qui souhaitent un dépistage vers les centres spécialisés s'ils doutent de leur santé après des rapports avec une personnes à risque. Nous avons ainsi reçu des messages électroniques anonymes dont les expéditeurs nous demandent des conseils sur la pandémie du VIH/SIDA. Août 2002 en avril 2004, des messages de Remerciements des personnes référées ont été reçu. Nous suggérons aux acteurs de la lutte contre le SIDA, la conception d'un site de rencontre, de sensibilisation et d'échanges sur la prise en charge et la stigmatisation des personnes vivant avec la pandémie du VIH/SIDA dans le milieu scolaire, universitaire et professionnel.

PP 1.3.

Serological Profiles in Hemodialysed Patients of Constantine

Semra Z, Ait Kaki B, Boulkhdra A. Laboratoire de Microbiologie CHU Constantine, Algeria

The serological diagnosis of the hepatitis B and C and HIV infection play a fundamental role in the screening of the asymptomatic seropositive and in patients exposed to infections risks.

A hundred and fifteen ser of dialysed patients of the university hospital of Constantine and Kidney clinic have been tested simultaneously in order to detect the Hbs ,HIV antigens and anti HCV antibodies

The used techniques are :

1- the ELISA test for the :

- Hbs antigen and the different markers (Ag Hbe,antiHbe antibodies,Hbc and antiHbs)
- Anti HCV antibodies
- And antiHIV antibodies

2- Confirmation tests:immunoblot

- Desiscan HCV for hepatitis C
- Western-Blot for HIV1 and HIV2

3- The PCR:the viral DNA in demand has been done in six(6) patients at negative serology in whome we find the noyon of viral hepatitis which is clinically declared.

Key-words:immunoblot-PCR-hepatitis B,C,-HIV-dialysed patients

PP 1.4.

Sero-epidemiological aspects of the HIV infection in Algeria

Ait Kaki B, Belabbes E, Bouguremouh A. Laboratoire de Microbiologie CHU Benbadis, Constantine & Institut Pasteur Virologie, Alger, Algeria

A sero-epidemiological study has been done as part of collaboration of microbiology laboratories of the university hospital of Constantine and the one of virology Pasteur Institute has report on sera of:

- 14685 consulting or in patients in the university hospital of Constantine (1985 -2003)
- 3000 pregnant women from Algier
- 2693 women from 40 districts of Algiers having received gamma globulin.

The exploitation of results of the study of 92 patients suffering from AIDS hospitalised in the University-Hospital has shown that the most raised frequency has been formed in the young adult (20-49 years) and the heterosexual way which dominates the infection way.

We notice that there is a local passing on (19 cases) in which (3) are from the south Algeria.

Key-words: serology -HIV -AIDS -epidemiology

PP 1.5.

Surveillance of HIV/AIDS. Epidemiological Trends. Cuba: 1986-2003

Rigoberto Torres Peña, J.J. Joanes Fiol, M.I. Lantero Abreu, G. Estévez.

Ministry of Public Health, National Aids Program 23th # 201, Vedado, Havana City Cuba. Zip Code 10400.

The Republic of Cuba, since 1986, established a National surveillance System that consists in confidential and voluntary screening of certain population groups thus reporting of Aids cases, deaths due to Aids and HIV-positive people. The higher rates of prevalence are found in the Western/Central areas of the country. This surveillance system besides from giving important information about prevalence and incidence has represented an opportunity to target educational messages to great amounts of people. The screening program has the main objective of detecting HIV-infected persons as early as possible, treating HIV-infection or mild symptoms in early stages and slowing or avoiding the development of full-blown Aids and the death due to the disease. By the end of 2001 all HIV-infected patients had access to treatment and mortality due to AIDS has decreased 18%. As a result of an uninterrupted work of screening with more than 29 165 207 HIV tests performed since January 1st 1986 through December 31, 2003 we have been able of identifying 5257 HIV-positive persons in a population of more than 6 million of sexually active population which represents a rate of serological reactivity of 0,01%. 79% of all detected cases are males and 85% out of this number are men who have sex with men being most the prevalent population group. We conclude that knowing the main groups affected by the epidemics of HIV/Aids as close as possible, a number of therapeutic and education measures can be taken. Our success in controlling blood-borne HIV transmission and mother-to-child transmission are good examples of the utility of an HIV surveillance system like this. With its opportune establishment, among other measures, like the existence of a strong National Program and a well structured Primary Care system we have been able to slower the course of the HIV/Aids epidemic that otherwise could have been several times bigger.

PP 1.6.

The vertical transmission of the pediatric AIDS in cuba

I. González, M. Díaz, J. Pérez

Instituto Pedro Kouri Ciudad Habana Cuba.

Background: A controlled program has been implemented at the primary health care level in Cuba since 1986 aiming to reduce the perinatal transmission of the HIV virus.

Methods: The program includes the administration of antiretroviral drugs to every woman who decides to continue her pregnant. AZT is the drug of choice used in a 500 mg daily from week 14 until the end of the pregnancy. Cesarean section is the most usual way of childbirth in these cases. During the first 6 weeks of life the child receives AZT in syrup (2mg/Kg/dose) every 6 hours. The evolution of these children is followed up in the pediatric outpatient consultation of Pedro Kouri Institute and are subsequently studied to determine whether they are infected or not by HIV.

Results: A total of 1086 seropositive women have been reported since January 1, 1986 to December 31, 2003 (20,6%) of all the seropositive, (1086/5257). One hundred thirty three (12,2%) of them have delivered a total of 138 children (5 women have delivered twice). Eighteen out of 138 are HIV+ (13,5%), 16 of them classify as AIDS (88,8%) and they have treatment, 9 with tri therapy, 2 are asymptomatic and 7 (38,8 %) have died. . There are 93 children with non-demonstrable infection using PCR and Western Blot assays (67,3%). Twenty-seven (19,5%) others children are still under study.

Conclusion: According to the facts presented here it may be considered that the Cuban HIV Control and Prevention Program is effective since the number of infected children remains low when it is compared to the figures of infected children from other countries

PP 1.7.

Correlation of HIV Prevalence Rates Between Sexually Transmitted Diseases Patients And Pregnant Women Attending Antenatal Clinic In India

Kant S, Shaukat M. All India Institute of Medical Science, National AIDS Control Organisation, New Delhi, India

Introduction: Patients with sexually transmitted diseases (STDs) are called "bridge population" because they acquire HIV infection from core transmitters (e.g. commercial sex workers) and transmit it to low risk population e.g. women in child bearing age. It is expected that STD patients would see the rise in HIV prevalence much before it is observed among pregnant women. We wanted to ascertain whether it was possible to anticipate the HIV prevalence rate among pregnant women if we knew the rate among STD patients. We therefore explored the correlation of HIV prevalence rates among these two groups

Methods: Twenty-six cities, spread over 23 of the 35 federal States of India, had both STD and ANC sentinel surveillance sites in the same city. Therefore, the source population in each city was assumed to be same for both types of clinics. STD was defined as a person having any one of the following; genital ulcer, genital wart, or cervical/urethral discharge. Antenatal women were those that attended antenatal clinic for the first time during the sentinel surveillance period. Sera for HIV was tested by unlinked anonymous method. Testing protocol was two ELISA or Rapid or Simple test. HIV prevalence data from 1999 to 2001 was analysed. The paired HIV prevalence rates were plotted as a Scattergram. Pearson's correlation was used to assess the correlation.

Results: With rising HIV prevalence among STD patients, there was a corresponding rise in HIV prevalence among antenatal women. HIV prevalence rate among antenatal women crossed one percent mark (i.e. generalised epidemic stage) when the prevalence rate among STD patients was more than 10%. However, the correlation was weak (Pearson's correlation coefficient (ρ) was 0.6).

Discussion: Only a small fraction of STD patients attend government operated clinic. Our inclusion criteria for STD were strict and hence non-ulcerative STD patients were not included. Hence STD patients included may not be true representatives of all STD patients. The direction of correlation though positive had weak correlation. The HIV prevalence rate among STD patients could be a reasonable indicator of prevalence rate among antenatal women.

PP 1.8.

The Rate of HIV/AIDS from 1987 to 2003 in Belarus and Influence of Injecting Drug Users on the Expansion of HIV Infection

Kaskevich IA. Vitebsk State Medical University, Belarus

Background:

Since the start of the epidemic, HIV has infected more than 60 million men, women and children and AIDS has cost the lives of nearly 20 million adults and children. Despite the intense international response to the HIV/AIDS pandemic, HIV continues to spread, causing more than 14,000 new infections every day, 95% of these are in the developing world. As it is the case with other infectious diseases, a safe, effective and available vaccine is ultimately required to complement and enhance the effectiveness of existing prevention strategies to control the HIV/AIDS pandemic, especially in developing countries.

Aim of study:

The aim of study was to describe the rate of HIV/AIDS from 1987 to 2003 in Belarus and influence of injecting drug users on the expansion of HIV infection.

Materials and methods:

Statistical data dealing with HIV/AIDS rate was studied. Demographic and epidemiologic features that we analyzed are age, gender and the place of living, education, social and material status.

Results:

For the period 2003 year, 2564 cases of HIV were reported in Belarus. We analyzed the disturbance of HIV patients during 1987-2003 years. We concluded that that HIV infection had 2 periods in Republic of Belarus. The 1st period of "relative well-being" lasted from 1987 to 1995. The 2nd period - the period of intensive epidemic process (from 1996). During the first period, the rate of new cases of HIV was from 5-6 to 20-21. Among HIV infected the most cases included foreigners that came in Belarus for studying (82-85%). During the 2nd period, the role of injecting drug users increased.

Conclusion:

1. The epidemiological situation in Belarus with HIV/AIDS is not favorable at present time. In Belarus, there is the high rate of HIV infection.
2. The first place on dissemination this infection is borrowed by Gomel region. Prevailing group on distribution of HIV infection is injecting drug users.

PP 1.9.

HIV Infection: present persisting problems for pregnant women and their babies and families

Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

HIV infection during pregnancy and developmental age is characterized by a strikingly different epidemiologic, clinical, and outcome scenario, according to our reference to Western countries, compared with developing world. While the systematical resort to an early diagnosis, potent anti-HIV therapy, cesarean section, and artificial feeding led to a nearly disappearance of novel cases of congenital HIV disease in developed countries, the enormous reservoir of HIV disease affecting whole generations of men and women during their reproductive age, strongly moves our attention to developing countries of SouthEastern world, where perinatally-acquired HIV remains a medical, social, and ethical challenge far to be resolved at this time. The strategies to prevent mother-to-child transmission of HIV, include primary prevention of HIV infection among parents, by promoting improved health care conditions; prevention of unwanted pregnancies in HIV-infected women; prevention of HIV transmission from infected women to infants. Moreover, we have to make our maxium efforts to ensure the survival of the mother and baby pair as far as possible, and to safeguard the family unit. A prevention phase should raise the level of awareness about HIV among young people in schools, military barracks, the countryside, and the villages, to promote a significant change in the behavior of the people towards HIV infection and its modes of transmission. A diagnostic phase should be aimed to early recognition of HIV disease. The treatment phase should include antiretroviral therapy and laboratory monitoring as currently feasible (even resorting to short-term simplified therapies), and possibly selecting more potent combinations for symptomatic women, with advanced HIV disease. Every HIV-infected pregnant woman should receive a specific information and counseling focusing on the rate of HIV transmission, and the strategy to reduce the risk, the potential effects of anti-HIV therapy during pregnancy, the schedule of monitoring, the need to resort to an elective cesarean section to reduce risks of transmission, and the need to avoid breastfeeding: babies born to HIV-infected mothers should be weaned with artificial milk up to the age of 1.5 years, although local situation often does not allow to renounce breastfeeding. The recent availability of multiple anti-HIV agents available through expanded access programs, are expected to help improve the present situation of childbearing women in the developing regions of the planet.

PP 1.10.

Temporal Trend of Fatality Events in a Cohort of 1, 214 Heroin Drug Addicts Followed Since 1977 in Bologna, Italy. Role and evolution of HIV-associated deaths

Manfredi R, Sabbatani S, Agostini D, Chiodo F. Infectious Diseases, University of Bologna, and Department of Public Health, Bologna, Italy

Aim of our study is to evaluate the temporal trend of deaths in an open cohort of i.v. heroin drug users followed in a large city of Northern Italy (Bologna), and to assess its relationship with HIV serostatus and AIDS, and the availability of potent antiretroviral therapies (occurred since mid-1996). One thousand and 214 i.v. drug users (heroin addicts), 916 males and 298 females, attending an outpatient service for treatment and prevention of substance abuse between 1977 and November 1996, were enrolled into our observational cohort, and their vital status was ascertained up to December 31, 2002. By matching demographical data with the registries of births and deaths of the Bologna metropolitan area, a retrospective research focusing on subjects who were still alive at December 31, 2002, was carried out. The great majority of enrolled subjects (>95%) were borne in the Bologna metropolitan area and surroundings. During the 25-year observation period, 271 i.v. drug users (22.3%) died, 211 males (23%), and 60 females (20.1%), but all deaths occurred after the year 1984. The general distribution of causes of death was significantly different according to patient gender ($p < .001$): AIDS-related deaths proved significantly more frequent among females, while overdose-related ones occurred predominantly among males ($p < .05$). The main causes of death were represented by: AIDS (52.8% of episodes), heroin overdose (22.1%), street accidents (7.4%), decompensated liver cirrhosis (6.3%), suicidal behavior (2.9%), homicide (1.1%), endocarditis and other heart infection (2.2%), pulmonary cancer or malignant lymphoma (1.8%), and pneumonia (0.7%). When considering our patient series according to HIV serostatus, we obtained a mortality rate of 43.5/1000 for HIV-infected patients, compared with 10.2/1000 for non-HIV-infected subjects. The highest absolute number of deaths was observed between years 1991 and 1996. The crude mortality rate for AIDS was 10.9% among males and 14.4% among females, while the rate of death due to other causes proved 12.1% among males and 5.7% among females. During the most recent years, a significant reduction in the number of AIDS-related deaths, attributable to the increased use of potent antiretroviral regimens, was recorded. When the life-threatening AIDS pandemic declined, a parallel drop of all other causes of death was also observed: however, the additional mortality rate remained higher, compared to that observed in the pre-AIDS era. During the whole analyzed period, the mortality rate for all causes remained greater for HIV-infected male i.v. addicts compared with females, but women aged 25 to 44 years represented the subgroup at higher risk of AIDS-related death. When excluding AIDS, all diseases involved as a cause of death in our cohort were predominantly present in the male component of our patient group, in particular in the age interval ranging from 25 to 44 years. In detail, the greatest mortality risk was observed between 25 and 34 years, while very few deaths were recorded before the age of 25, and after that of 45 years.

PP 1.11. Introduction to Risk Mapping and Behavioural Analysis as Tools to Fight against STI/HIV/AIDS: the case of Douala Cameroon

Jeanne d'Arc Kengne. Association Culturelle Mission de Recréation (ACMR), Douala - Akwa Douala, Cameroon

Introduction to Risk Mapping and behavioural analysis as tools to fight against STI/HIV/AIDS: the case of Douala Cameroon

Introduction :

Since the year 2000, the UNICEF Cameroon has introduced Risk Mapping (The cartography of vulnerability), life skills and the behavioural analysis in the programme of education and prevention of the youth from HIV/AIDS in and outside schools.

The youth friendly centres - Centre d'Information, d'Education et d' Ecoute des jeunes (CIEE) - and local information pools are expression structures created for the application of these tools. We have the dialogue structure which is the health club formed by the youth.

These clubs which are usually vulnerable groups are managed and run by dynamic youths from the same neighbourhood called Leader peer educators. They consider the solutions to apply to their particular problems and develop strategies to stamp out all negative behaviour while at the same time encouraging their peers to join these clubs.

The CIEE of the NGO named ACMR for which I work has experienced these tree tools or instruments since the year 2000 with 5400 young people.

Description :

The analysis of the local maps showed the various risky factors that expose young people to HIV/AIDS infection: video-clubs, bars, nightclubs, game houses, guesthouses... are attraction areas for them. They use school premises, churches and markets as areas of rendezvous.

The result of the behavioural analysis shows that: the youths identify themselves to the project, own it and bring out from the risky factors they have identified the risky behaviours that they need to change to be healthy. They have also identified through life skills which positive behaviours to promote or develop. They also identify leaders or institutions that can help them to achieve the positive behaviours desired. Through their health clubs, they choose which active methods could be used to learn these skills.

Lessons learned:

The behavioural analysis is for us a life instrument that enables young people to feel very concerned by the STI/HIV/AIDS problem, to be aware of it, to be motivated for the change of behaviour and finally to decide efficiently by themselves how to solve the problems they meet.

Conclusion :

Finally, these minimum packages of activities with the youth contribute to the creation of a favourable environment for the participation and development of adolescents in attenuating their vulnerability particularly to STI/AIDS contracted following risky behaviours.

PP 1.12.

Pluses of HIV/AIDS Peer education Training For Adolescents In Uganda.;A Case of the AIDS Challenge Youth Club

Sentamu SPS, Lukwago BL.The AIDS Support Organisation, Kampala, Uganda

Introduction: The aims of the training were: (i) skills training endowment in decision-making and self assertiveness: (ii) sensitisation of members to the feelings and needs of persons living with HIV in order to improve their willingness to care for these individuals. (iii) to reinforce and intensify precise knowledge concerning STDs and HIV disease

Method: 493 adolescents from 7 districts participated in a five day residential training workshop which included lecture, discussions, games, role play and interactive demonstrations. The workshop was evaluated by means of pre-and post tests surveys and focus group interviews.

Results: Scores on pre and post tests from the workshop showed significant gains in the students reported attitude to possible future encounters with HIV positive persons including family members and teachers and peers. Awareness about AIDS knowledge were very low especially because of cultural beliefs and general social suppositions. At the end of the course the students expressed self-assurance to tackle their roles as peer educators.

Conclusion: The contribution in the training of young people living with HIV played a noteworthy role in helping the fellow participants comprehend the reality of the disease. All 493 persons who were trained are peer educators in their communities and respective schools.

The Post training peer education field experiences revealed that more youth were seeking health services especially testing for sexually transmitted diseases including syphilis, Gonorrhoea and HIV.

PP 1.13.**Health Seeking Behaviour-Means of Stimulating Youth Into Seeking It?**

Sentamu SPS.The AIDS Support Organisation, Kampala, Uganda

Introduction: Young people are continuously being infected with HIV and other STDs not because they do not know the perils of the disease but because they do not have an inherent behaviour pattern that seeks health knowledge/treatment.

Methods: Two-day holiday workshops for the youth are organized three times a year with fifty participants or more by the AIDS challenge youth club (ACYC) with the objective of enhancing HIV/AIDS knowledge for the youth as well as fundamentally inducing the youth to seek information about their health. A Facilitator well conversant with the subject matter is employed for the workshop. Voluntary counseling and testing is one of those areas that are focused. It is relayed to the youth during AIDS talks and or seminars and also by the use of radio programmes and through peers.

Results: A lot of reproductive health information including HIV/AIDS is given out to the youth but there are more questions as pertains to voluntary counseling and testing which exudes the fact that there was either little or no information for the youth about voluntary counseling and testing.

A lot of programmes are hinging on reproductive health but always abandon to mention the importance of voluntary counseling and testing for the youth and reproductive health

The youth receive information regarding all aspects of health needs for youth as well as promoting health-seeking behaviour.

Discussions: There's need to employ volunteers as facilitators for these workshops because of the fact that youth easily identify with fellow youth or those who tend to have youthful traits.

There's need for complimentary site visits to health centers so as to give youth first hand information.

There's need to introduce a program on the same in schools that are disadvantaged by location and site.

PP 1.14.

The Professional Insertion of AIDS-infected Young Girls

Muyuku EM, Munyana MM. Swaa-Burundi, Bujumbura, Burundi

Background: One of the strategies adopted by SWAA- BURUNDI in order to reinforce the abilities of aids infected girls is the professional active insertion which has been initiated since January 2001.

Methods: Identification (selection) of those who need to be helped among the young who are formed by SWAA- BURUNDI. an individual interview should be carried out in order to put them into groups or categories according to their educational level (computer, artistic skill, cooking), knowledge on aids, responsible sexuality, pills and prostitution.... the program should also cover the rural regions where 260 young girls would yearly take advantage of such an education. sensibilisation for the burundian young.

Results: - Knowledge acquisition and abilities in different domains such as computer, artistic knowledge, Aids realities and means of protection or prevention.
40 young girls have already been formed. 20 young girls have already been inserted in professional activities.

Conclusions: The professional insertion of aids infected young girls is the best strategy for fighting poverty, aids and sexually-transmitted diseases (STDs). The recruited and formed young girls will in return be our representatives in their working places.

PP 1.15.

The Role of Religious Doctrines in Prevention of AIDS

Esmaealzadeh M, Ghanbari M. Mashhad University of Medical Sciences, Mashhad, Iran

Issues:

AIDS is a biopsychosocial problem. If we don't consider the psychosocial dimensions of AIDS, our biologic plans will not be effective.

Role of religious centers is development and education of the human values and traditions.

There are several ways in which religions have an impact on AIDS prevention education. For example, homosexuality is seen as immoral and unnatural in Islam. Too, Islamic leaders disapproved of any form of sexual behaviors outside of marriage.

Description:

Some say "condom" is an effective way for HIV prevention. It's correct. But it isn't a final solution for AIDS. Final solution is "behavior change".

Some people consider the simple ABC approach to AIDS prevention (Abstain, Be faithful and Condom).

There are experimental samples of faith-based initiatives that the role of religious leaders and organizations in AIDS prevention has had major impact: Uganda, Senegal and Jamaica.

We see a pattern of behavioral changes compatible with the prevention strategies favored by Islam. For example: Early age of sexual debut among youth and to have multiple partners are 2 important problems in control of AIDS. Islam tells people they should be abstinent and constant. Abstinence causes delay of sexual debut among youth and fidelity causes reduction in the number of sexual partners. They are 2 main factors for HIV prevention.

HIV+ people in Iran are less than in many countries. Because most people in Iran are Muslim and implement Islamic doctrines.

Lesson learned:

For HIV control, only implementation of biologic plans isn't effective. Too, we should consider psychosocial plans especially by religion for HIV prevention. Because AIDS is a biopsychosocial problem.

Recommendation:

We recommend:

- 1) Attention to religion for having active role in HIV prevention
- 2) Establishment of national and international AIDS organizations include physicians, socialists and religious leaders
- 3) Development of religious education in schools and universities
- 4) Using software prior to hardware for HIV prevention

PP 1.16.

The Role of IV Drug Users`s Control in Prevention of AIDS

Ghanbari M, Esmaeelzadeh M. Mashhad University of Medical Sciences, Mashhad, Iran

Issues:

Drug addiction and AIDS are the most serious health problems facing the world today. Almost of people involved (75-90%) to these problems aged 20-45 years, that is time of development, blooming and social activities, Also numbers them are to growing. Many of social crimes (robbery, felony..) are related to the addiction, But there is an important subject about addiction, Relationship between prevalence IVdrug using (IVDUs) and raising incidence of HIV, because the main way for HIV transmission is IVDU in many countries.

Description:

Iran has about 3 millions drug addicts that about 300000 of them are IVDUs, a reason is neighbours with the largest source producing opium and other narcotics in the World (Afghanistan). Most of IVDUs have a low cultural and economic level, corruption and irresponsible in ethic, that Infected IVDUs can transmit AIDS by high risk sexual behavior in addition to injecting way with contaminated shared syringes. It means they are hidden HIV source for community. With due attention to over 65-70% of HIV transmission is by IVDUs in Iran, control of them have a great role in prevention of AIDS.

Lesson learned:

One of important ways for prevention of social crimes in many developing countries is control of IVDUs.

According to this research, Recommend:

- 1) Education to afflicted HIV and high risk people about: complications and transmission ways of AIDS (esp risks of IVDUs)
- 2) Use of international experiences and programs (needle exchange, bleach programs, abstain, faithful to wife, use condom,..) and a global campaign against HIV and addiction (esp IVDUs)
- 3) Learning parents, social and religious native leaders for supervision and emotional support of youth
- 4) Collecting drug addicts for giving up addiction then support socioeconomically them

PP 1.17.**Screening of Iranian Blood Donors for Transfusion Transmitted Infections**

Moniri R., Mossavi G.A. Kashan University of Medical Sciences, Iran

Abstract

The transfusion transmitted infection is potentially dangerous complication of transfusion therapy in Immunocompromised patients.

The aim of this study is to determine the prevalence of transmissible diseases in the blood donor population in Kashan-Iran.

A total of 600 consecutive sera were tested for CMV-IgM antibody, HBsAg, Hepatitis B core (HBc) antibody, Hepatitis C (HCV) antibody, HIV antibody, and RPR with standard methods.

Of the sera tested, 14 (2.3%) were found to be CMV-IgM positive. The frequency of seropositivity revealed no significant differences between male and female donors. The frequency rates of CMV-IgM seropositivity tend decline with increase of the age of the donors. There was no any relationship between the frequency rates of CMV-IgM seropositivity with the educational level, socioeconomic status, single and married, urban dwellers and rural residents. Prevalence of HBV, HCV, HIV and RPR being 0.5%, 0.5%, 0 and 0 respectively. In addition, the prevalence of HBs Ag, antibody to hepatitis C virus were compared between CMV seropositive and seronegative groups.

These findings have important clinical application, because the detection CMV positive sera may reduce the risk for transmission of CMV in blood and thereby also decrease the risk for CMV-induced complication.

PP 1.18. Prostituées de Rue et VIH : interactions sexuelles et logiques de gestion du risque

Germain Trottier, Dominique Damant¹, Ginette Paré³, Nolwenn Doitteau³, Lina Noël², et Michel Dorais¹

Laval University, School of Social Work, PAV DKN, L-3475B, Quebec (QC) G1K 7P4

Problématique: Une recherche antérieure ayant mis en lumière le rôle de la violence dans la transmission hétérosexuelle du VIH-sida chez des femmes vivant dans un univers à risque, nous avons poursuivi la réflexion et examiné les stratégies préventives auxquelles ces femmes recourent pour contrer le VIH. A cet égard, la recherche actuelle a investigué le vécu sexuel de femmes prostituées de rue, dans le contexte de leurs rencontres sexuelles privées et commerciales. **Méthode :** L'étude a été réalisée conjointement par deux équipes de recherche de l'université Laval subventionnées par le FQRSC et le FRSQ. Vingt répondantes volontaires répondant aux critères de sélection ont été recrutées auprès de deux organismes oeuvrant dans les quartiers centraux de la ville de Québec. L'approche biographique a été retenue comme cadre théorique; la collecte de données a été faite au moyen d'entreviens semi-directifs; l'analyse de contenu thématique a été privilégiée pour traiter qualitativement les données.

Résultats : Trois constats principaux sont à mentionner :

- 1) les personnes rencontrées n'adoptent pas nécessairement des conduites sexuelles à risque lors des rencontres sexuelles commerciales;
- 2) leur façon de gérer le risque consiste à utiliser généralement le condom comme moyen de prévention et comme barrière physique et psychologique pour exercer le métier; et
- 3) quatre logiques d'action expliquent la non protection :
 - a) la protection impossible lorsque ces femmes se retrouvent en situations d'agression,
 - b) la protection zéro quand la toxicomanie occulte toute notion de risque,
 - c) la protection irrecevable quand la velléité de protection est gommée par l'affect, l'amour notamment et d) la protection inconcevable où la représentation de la maladie est minimisée, sinon supprimée, par l'idée qu'elles ne sont pas à risque.

Conclusion : Les prostituées de rue connaissent bien les modes de transmission du VIH et les moyens de se protéger. Émergent cependant de leurs expériences de vie et de leurs représentations de la sexualité, des conditions qui les rendent plus vulnérables au VIH. Au-delà des soins médicaux, il importe de leur offrir du soutien psychosocial et des activités éducatives de prévention tel que prôné par des modèles d'intervention centrés sur la vulnérabilité du corps en danger, tant du point de vue de la cartographie personnelle de la prise de risque que du point de vue interpersonnel.

1.École de service social, Université Laval.

2.Équipe de recherche du FRSQ sur la prévention des ITS et du VIH-sida.

3.Équipe de recherche interdisciplinaire sur la violence familiale et la violence faite aux femmes (Cri-Viff) Université Laval.

4.Direction de santé publique de Québec et Institut national de santé publique du Québec.

5.Damant, Trottier et al., (2003). Femmes, violence, ITS-/sida. École de service social et Cri-Viff, université Laval.

PP 1.19.

Sexual Behaviour of Female Undergraduates in The Freshman Year At The University Of Ibadan, Nigeria

Faseru B, Sangowawa AO, Okoro CA, Lawoyin TO. University College Hospital, Ibadan - Nigeria

Background: For biological, economic and social reasons females especially adolescents and young adults are vulnerable to sexually transmitted infections including HIV/AIDS.

Method: This study was conducted among the female undergraduates in the freshman year to assess high-risk sexual behavior among them. Using self-administered questionnaire, all the new female students who registered at the University Health services were enrolled.

Results: Age range of respondents was 16-30yrs (mean age 20.3 ± 2.6). Of the 223 students seen, 157 of them (70.4%) had never had sex. Lowest age at sexual debut was 9years (Mean age 19.3 ± 3.4). Early sexual activity was associated with an increased number of lifetime sexual partners ($p=0.008$). Of the sexually experienced, 50(75%) had their first sexual contact with boyfriend, 11(16.7%) with casual friend, 2(3%) had sex with older men for money and 3(4.5%) were victims of rape. Most of their sexual partners (79%) were between ages 20-29. At the sexual debut, 38 out of 66(58%) did not use condom. In the last 1 and 12 months, 40.9% and 56.1% respectively had sex. Number of their sexual partners within that period ranged from 1-4. At present 62.1% use condom while only 14.6% reported using it always. Thirty-seven (56%) of them have ever had one sexual partner, whereas one (1.5%) has had 10 sexual partners and another one (1.5%), 11 partners. Majority of those that claimed to have single partners could not vouch that their male partners did not have sex with another person apart from them.

Conclusions: This study shows a large proportion of female students have not initiated sex before entering university. However, high-risk sexual behaviour is still prominent among the sexually active. Family life education must continue at this level to reduce high-risk sexual behaviour thereby preventing HIV/AIDS

PP 1.20.

Epidemiological Features of Tuberculosis in Northern Italy, and Public Health Care Correlates

Manfredi R, Sabbatani S, Legnani G, Chiodo F. Infectious Diseases, University of Bologna, Italy

Tuberculosis (TB) is borne by increasing morbidity-mortality rates both in industrialized and developing countries. Changes in epidemiology patterns, atypical manifestations, and the spread of chemotherapy-resistant strains, are prominent problems. The recent variation of a number of predisposing factors are altering TB epidemiology and presentation: the HIV pandemic, advancing age and concomitant illnesses, increasing immunodeficiency, alcoholism and drug abuse, and especially immigration from regions where tuberculosis is endemic, or predisposition to acquire TB after arrival in Western countries, due to overwhelming social-economic problems. An analysis of patients (p) hospitalized from 1996 in Bologna, allowed us to identify 90 consecutive p with confirmed TB. These 90 episodes were evaluated on the ground of several variables, to compare the disease features between Italian and extra-Western Europe p with TB who came to our attention in this 6-year period. When considering demographic-epidemiologic data, significant differences were found among the 62 Italian p, and the 28 p coming from extra-Western Europe countries (50% from northern Africa). When compared with foreigners, Italian p had a greater median age (51.7 vs 29.9 years; $p < .001$), and more frequent and varied underlying disorders (prior diagnosis or familial history of TB, chronic pulmonary, heart, liver, or kidney disease, diabetes, malignancies, collagen vascular and bowel inflammatory diseases; $p < .05$), a higher incidence of HIV/AIDS (31.1% of Italian cases; $p < .001$), with a predominant pleuro-pulmonary localization compared with lymph node and/or disseminated ones among HIV-infected p vs non-HIV-infected p ($p < .01$). Immigrants had more frequent generic risk factors (low income, social-economic problems, cigarette smoke, and drug-alcohol use; $p < .05$ versus Italian patients). No appreciable difference was found as to lung radiological findings between the 2 study groups: disease presentation proved different only according to an eventual HIV disease. Because of older age and concomitant disorders, Italian p remained hospitalized for a significantly longer time vs foreigners (52 vs 27 days; $p < .001$). Our 6-year experience shows that 2 different disease patterns of TB may be observed in our metropolitan area. While immigrants are usually represented by proportionally young, otherwise healthy p with predominant lung localization, Italian p are mostly represented by elderly, with underlying diseases and specific risk factors for TB, a more frequent HIV co-infection (and a more common involvement of sites other than lower respiratory tract). The epidemiologic-clinical features of our 90 p with a confirmed TB, reflect a clearly distinct disease profile between immigrants and Italians p, but we cannot exclude that the significant spread of TB, the continued immigration, and growing predisposing conditions in the general population, may lead to a further increase of diagnoses, especially towards extreme life ages, which could either prompt, or may be a consequence of a progressive change of demographic and predisposing conditions. Surveillance and preventive strategies of screening, diagnosis, therapy, and control of TB need an update, to avoid the spread of TB, due to the merging of risk factors of immigrants, with supporting factors of the local population, which is expected to prompt a health care emergency in inner cities, where integration of immigrants may meet exposed and vulnerable native population. Physician awareness of TB should be improved, especially when high-risk p are of concern, in order to obtain a rapid diagnosis and cure, and reduce transmission.

PP 1.21.

International Charity Organization "Rehabilitation Center "STEPS", Vinnitsa branch, Ukraine, Activities

Vlasova N. Vinnitsa Branch of International Charity Organization "Steps", Vinnitsa, Ukraine
Vinnitsa Branch of International Charity Organization "Rehabilitation Center "Steps" started the activity in 2001 in reply to HIV/AIDS, and substance abuse epidemic spreading among Vinnitsa and region population.

The main goal of "Steps" activities are social support and charity of the community socially unprotected strata, homeless, people with substance abuse problems, AIDS cases, HIV-infected people, psychological and social rehabilitation of those people and their family members; science and education development; scientific, research programs realization in the psychology, psychotherapy, HIV/AIDS and substance abuse spheres in collaboration with state establishments and NGOs.

Activity in the sphere of HIV/AIDS.

- Preventive measures among injection drug addicts;
- Preventive measures among pupils and students;
- Psycho-social rehabilitation of injection drug addicts, being and not being HIV-infected;
- Collaboration with the specialists of state establishments (Medical University, Narcological Dispensary) for HIV, drug abuse' scientific studies implementing;
- Research projects' carrying out.
- Preventive measures "Equal to Equal" implementing;
- HIV/AIDS test-retest counseling; assistance for HIV/AIDS examination;
- People with HIV, members of their families' counseling.

Target groups:

- People with substance abuse problem;
- Co-dependent people;
- People living with HIV;
- Close surrounding of people living with HIV;
- Children of families with substance abuse problem;
- Pupils and students.

Services:

- Psychological and social rehabilitation;
- Inpatient clinic for 15 cases;
- Test-retest counseling;
- Body-oriented therapy;
- Art-therapy;
- People with substance abuse problem, collaterals spiritual, sex and family education;
- Individual, and group counseling;
- Self-help groups;
- "Anonymous Alcoholics", "Anonymous Drug Addicts", community support;
- HIV, sexual tract diseases, preventive and educational measures (trainings, focus-groups, presentations, workshops);

Researches had been carried out:

- Statistic data and official information gathering and administration.

Projects' carrying out:

- Hospital versus Outpatient Alcohol Abuse Treatment in Vinnitsa, Ukraine.
- A School-based HIV/AIDS Educational Intervention in Vinnitsa, Ukraine.
- Feasibility of Antiretroviral Therapy in Vinnitsa, Ukraine.
- HIV Prevalence, Related Knowledge and Behaviour among Female Sex Workers of Vinnitsa, Ukraine.

Sponsor: International Fogarty Center, University of Alabama at Birmingham, USA;

Trainings:

- HIV preventive measures among injection drug addicts;
- Preventive measures among pupils and students;
- Psychological adaptation of people living with HIV, members of their families;
- Leaders from people had completed rehabilitation program, HIV-infected, training for self-help groups leading;
- Partner communication;
- Creativeness;
- Personal growth;
- Volunteers training;
- Fundraising, research projects applications writing (in collaboration with the employees of Medical University).

Planes of organization:

- Psycho-social and medical aid for people living with HIV/AIDS;
- Preventive literature issuing;
- Information-educational trainings regarding HIV, sexual tract diseases of different strata of the society and employees of schools, colleges, clinics' implementing;
- Information-counseling service regarding HIV, sexual tract diseases foundation;
- Summer therapeutic camp for people with substance abuse, HIV problems, and co-dependent on (adults, adolescences and children);
- People with substance abuse problem, HIV, co-dependent on works permanent exhibition.

PP 1.22. Evolving Assistance Features at an Infectious Disease Day-Hospital Service, in Relation with the Natural History of HIV Infection in the Highly Active Antiretroviral Therapy (HAART) Era

Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

In order to assess the frequency and features of admissions carried out at a four-bedded Infectious Disease Day-Hospital service in Northern Italy, a retrospective evaluation of all admissions carried out in the last decade (1994-2003) was performed, on the ground of their clinical and assistance features, and the predominating disease, represented by HIV infection. During the period preceding HAART introduction (years 1994-1996), the proportionally low mean number of admissions (110 per year), was highly linked to the remarkably elevated prevalence of HIV disease and its complications, which accounted for 89.4% of Day-Hospital hospitalizations, their recurrence, and their prolonged duration. Immediately after HAART introduction, the number of Day-Hospital admissions showed a progressive and significant increase, from 171 in the year 1997, to 318 in 2002, and 338 in the year 2003 ($p < .0001$ versus the pre-HAART era), although this phenomenon paralleled a concurrent drop of percentage of HIV-related admissions (from 59.1% in 1997, to a minimal value of 25.6% reached in the year 2001; $p < .0001$). In fact, while HIV-associated hospitalizations decreased, a significant temporal increase of admissions due to chronic liver disease (from 44.4% of patients followed in the year 2000, to 57.9% of 2001, and 58.1% of 2003; $p < .0001$). Concurrently, the progressive reduction of duration of admissions allowed a significant increase of overall number of hospitalizations performed in each examined year: from 2478 in the year 2000, to 3054 in 2001, up to 3348 in the year 2003; $p < .0001$), and the mean bed occupation rate showed a continued rise, as expressed by a figure increasing from 8.2 in the year 2000, to 10.1 in 2001, 10.9 in 2002, and 11.1 in the year 2003 ($p < .0001$), leading to index of mean bed occupancy to 284.3% compared with that of year 2000. The rapid and notable modification occurred at health care assistance of our Day-Hospital service during the last years are largely attributable to the significant changes occurred in the spectrum of infectious disorders which came to our attention during a decade of monitoring: actually, from a situation of a low number of prolonged hospitalization typical of patients with advanced HIV disease, the HAART era led to a progressive broadening of the spectrum of disease, and a notable reduction of admission time. Notwithstanding this situation, no significant modifications were observed as to mean weight of diagnosis-related group (DRG) features: from a mean 1.03 figure per patient registered in the year 2000, to a mean 1.02 figure in the year 2003. This last feature depends on the maintenance of proportionally elevated DRG values related to HIV disease mostly complicated by opportunistic infections and/or malignancies (1.5 ± 0.4), and the adjunctive clinical impact determined by a growing number of decompensated liver cirrhosis (mean DRG value of 1.0 ± 0.5). In conclusion, the evolution of health care assistance features in an Infectious Disease Day-Hospital setting, seems strictly linked to the progressive modification of prevailing disorders. Even though assistential resources (i.e. available beds and dedicated professional assistance), remained exactly the same, during the past decade a significant enlargement of disease spectrum, and a progressive increase of absolute number of hospitalizations and occupancy and turnover rates, were found. A careful and permanent monitoring of the features and modes of health care provision at a reference Infectious Disease Day-Hospital service may allow to take into account of significant temporal modifications, and contribute to ensure adequate assistential planning, including the eventual revision of structural, professional, technical, and funding resources.

PP 1.23. To Foster Awareness Against AIDS

Sarker AH - Physiotherapy Center, 44/8 West Panthopath, Dhaka-1205, Bangladesh

Introduction:

Sexually Transmitted Disease (STD) like Gonorrhea and Syphilis- the AIDS also sexually transmitted disease. The causative organism is RNA virus. So the affected person is unable to stand against any kind of infection and ultimately succumb to death. The affected person may suffer from chronic diarrhea, chronic cough, fever etc. and rapid deterioration of health & weight loss.

The routes of entry of the virus are Unprotected sexual contact; Oral contact by the AIDS patient, Sexual rectal contact by the affected person; Accidental introduction of contaminated syringe; Accidental transfusion of blood to a person from AIDS patient; Maternal transmission.

Treatment:

Bangladesh believed to be the country with 13 thousand of people living with HIV. Prevention is only better than cure. Treatment of HIV patients requires a detailed knowledge of the disease and introduction of the new drugs. Prevention by Foster Education and Awareness Against AIDS.

Results:

The person who are mostly affected are Drug addiction specially young group and teenagers; Promiscuity; Free sexual customs. The drivers are also affected. The affected person is unable to stand against any kind of infection and ultimately succumb to death.

Conclusion:

The treatment of the disease is very costly and complicated moreover out of reach of the common people. So social awareness about this dreadful dangerous disease is very important and only solution is prevention. So to Foster Education and Social awareness may be done against AIDS by wide publicity by media like radio, television, newspaper, posturing, short film in the cinema hall and also make public awareness by health workers in villagers & urban area.

PP 1.24.

Immigration and HIV Infection in Northern Italy. Inpatient Admissions, 2000-2003

Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

Immigration is a proportionally recent phenomenon in Italy. Caused by the sudden and unexpected arrival of waves of foreign citizens, refugees, individual escaping from war scenarios, and their families, it is of great concern due to the socio-economic, cultural, and also health care impressive impact. A prospective survey of all clinical charts of patients hospitalized or followed on day-hospital basis at our Infectious Disease Unit until the year 2003, allowed us to assess the frequency of admission of patients immigrated from extra-Western Europe, and to analyze all available variables according to a series of epidemiological and clinical parameters, and the eventual retrieval of HIV infection. The rate of patients immigrated from extra-Western Europe showed a significant increase among our inpatients, and at a lesser extent and later during time for day-hospital hospitalizations: 8% and 4% during year 2000, 11.3% and 6.6% in 2001, 15.2% and 9% in 2002, up to 23.9% and 10.6% in 2003 ($p < .0001$ for inpatients; $p < .007$ for the day-hospital-followed individuals). Nearly 60% of patients came to our attention from Africa (Morocco, Tunisia, Eritrea, Ethiopia, Somaliland and Nigeria as the most represented countries), followed by Eastern Europe (Ukraine, Russia, Belarus, Croatia, and Poland), Asia (Pakistan, Sri-Lanka, Bangladesh, and China), and America (Caribbeans and Argentina). When comparing the admission features of citizens from Western Europe with those of patients coming from abroad, no differences were found as to duration and intensity of assistance, with HIV disease prevailing among regular admissions (38.8%), and day-hospital access (40.8%), followed by acute-chronic liver disease, central nervous system and respiratory tract infection, and sexually-transmitted diseases. HIV-infected immigrants are frequently (62.6%) AIDS presenters (i.e. subjects who disclose their HIV serostatus concurrently with a diagnosis of full-blown AIDS), but less than 5% of these patients are already on antiretroviral therapy. While the frequency of HIV associated admissions did not show temporal differences in the considered period, immigrants subjects had an increasing frequency of tuberculosis, skin and soft tissue infection, exanthems of different origin, gastrointestinal disease, parasitic diseases, and malaria ($p < .05$ to $< .0001$). In conclusion, the major impact on inpatient admissions of patients immigrating from extra-Western Europe, is due to the frequent access through the hospital Emergency services. The persistence of HIV infection as the more common diagnosis in immigrated patients, recommends to carry out an informed screening, while a continued monitoring of this expanding phenomenon is strongly needed, in order to improve a sustainable social and cultural network, to plan health resource allocation, and to refine appropriate and targeted preventive strategies.

PP 1.25.

Disasters on Medications and Technical Behaviour Condition

RoseJoshi

37/74, Gucharangalli, Omnagar

sinamangal-9

Kathmandu,

Nepal.

Being as an Author its self HIV positive I would like to feel to work with +ve group so I joined the group called Prerana which means Inspiration in Nepali. After working long year I had elected as coordinator of a National Network of People Living with HIV/AIDS in Nepal (NNP+N) than I started to work for network since than to till to this day I have been working as a coordinator for NNP+N.

Scenario being unnoticeable by Government as well as the way behaving by technical medical persons who caused exists of stigma and discrimination so people afraid to front to say that they are positive and even many of them doesn't have a knowledge about ARV/ART. AIDS is a political and business issue for all of them so it has to protect at any cost. No such a good leader, commanders, or monitors has been productive in my country.

We could have to change a whole system of my country for HIV issue in this situation all of them were ridiculous from upper level to higher level at all level and they even doesn't understand the what does stand a word for PLWHA it is a shameful for our Health Ministry who raise this question about the meaning of PLWHA so many thing being so uninfrastructures which makes senseless and frustration. Even if you go to the hospital the way they treat was indigestible which gets sometimes to illuminate of a hum inlet front others it's a panic for HIV positive so LETS GIVE THE HIV/AIDS A HUMAN FACE.

PP 1.26.**Stigma Attached to HIV / AIDS : Implications for Health Care and Social Adjustment in Mumbai**

Chauhan SL. National Institute for Research in Reproductive Health, Mumbai, India

The broad objective of the study was to assess the nature of stigmatization, discrimination and denial occurring in relation to HIV/AIDS in different settings and how it affects the individuals with HIV/AIDS in relation to seeking health care and social adjustment. The findings of the study will fill important gaps in the current knowledge and provide critical information for the design of strategies for overcoming the effects of HIV/AIDS related stigma. The qualitative and quantitative research techniques that were used to elicit responses included in-depth interviews of HIV sero-positive/AIDS patients (N=91); care-givers at hospital (N=60), at home (N=20), counselors (N=20) and interviews of persons representing general population (426 households).

The salient findings of the study indicate that 43% of 91 interviewed persons living with HIV (PLWHIV) have not revealed their sero-positive status to any of their family members, workplace or in the community. The main reasons being fear of being thrown out of house or the community and fear of losing job. The remaining PLWHIV shared their HIV status with either of their spouse, parents, relatives and friends. The experienced various types of reactions at home and in the community

In the hospital and clinic settings, PLWHIVs perceived reactions in many forms. Among them 50% experienced sympathetic attitude, mostly from Doctors while others respondents perceived negative reactions. The negative reactions were fear, anger and hate more at the hands of attendants. Among many reasons, the major reason for the negative reactions was fear of getting infected. Eighty percent employed respondents have not revealed their HIV status at workplace, the major reason reported was fear of losing the job. Majority felt that they contracted the infection through high risk sexual behaviour. Majority of female PLWHIV felt that they were infected by their husbands. Majority were not satisfied with counseling, particularly post-test counseling. They demanded quality counseling also for their family members, particularly to their spouse.

The study findings indicate that stigma and discrimination are experienced in many forms by the PLWHIVs. The study explores that "fear" is the major factor for existence of discrimination, particularly among health care providers. Fear of getting infected and since it is not curable, the fear of death looms large in their minds.

PP 1.27.

The Problems and Effects of Mother to Child (MTC) HIV Transmission in an Extended Family System in Ghana

Duodu MO, Osei-Ntim O, Agyekum D, Afriyie KO, Amponsah G. Beware of AIDS (BAWA), Manchester, UK

Introduction: Mother to child transmission of HIV accounts for the highest single mode of infection in children in Ghana. The extended family system create an avenue for interference in decision making by women and almost wipes away their privacy and freedom. It is worse if the economic status of the woman is not all that sound or the woman depends on family members, particularly among her in-laws.

Purpose: The aim of this paper is to bring out some of the problems women encounter in their fight against HIV/AIDS in communities where not much has been done known about the pandemic. Most women believe in our local traditions from which it is derived that "a woman is supposedly, placed under the cover and care of the husband".

Method: This tradition believes that it is the responsibility of the man to provide all that the woman and her children need. In the pursuit of this some men have added to it, the right to make decisions for their wives and unfortunately in some cases concerning testing, breastfeeding, baby-care, participation in programmes on HIV/AIDS' awareness, education etc. Some of these decisions are influenced by in-laws and this is where the social stigma set in.

It is on record that awareness and testing is higher among pregnant women, educated women and women who have access to communication like the radio, television and other audio-visual equipments at home and also those in constant contact with healthcare practitioners and providers. A more careful look at some of the HIV messages from our local people who have not had current and frequent interaction with new developments on the HIV, tell you disjointed stories combined with taboos and denial stories. This has added to the fear associated with HIV and its Stigma.

Conclution: Women in the low income group and those without any meaningful source of income and therefore depend on their spouses and families are the most vulnerable to the HIV/AIDS' infection. They have not only accepted decisions on their health from their husbands and in-laws but also have almost lost their rights to decide on issues concerning their in-born and newly-born babies. To minimise MTC transmissions, we need to step-up our Information, Education and Communication (I.E.C) programmes and involve the communities in whatever programmes members of the community would be involved in and educate them on local, easy to operate small-scale businesses. This would help them to be independent economically and socially and would offer them the freedom to decide the direction of their individual lives.

PP 1.28.**The Economic and Educational Problems of HIV/AIDS' Infection in Rural Ghana**

Duodu MO, Mohammed MY, Osei-Ntim O, Adusei K, Amponsah G. Beware of AIDS (BAWA), Manchester, UK

Introduction: This paper is aimed at unearthing the psychological effect of HIV/AIDS on both the individual victim and the family. By virtue of the extended family system, the assets and liabilities of one family member is entirely the responsibility of the extended family. An HIV victim is a responsibility for the entire family.

Methods: Stress is piled on an HIV/AIDS' infected person and family for three main reasons. The first cause of stress is fear the of death facing victims, as there is no known cure yet. The second is the victimisation and stigmatisation to the extent that people get stigmatised for being in contact with an infected person. Thirdly, there is lack of finance to take care of the infected person, his responsibilities and dependants.

Results: The absence of a medium to share one's problems, breed frustration which in turn manifests in the rather faster deterioration of the physical and mental appearance of victims and some how affect carers and dependants. Experience has shown that in areas of less stigmatisation, people share their problems and even though there is no cure yet, victims avoid slumping down physically and mentally. Mental pain and for that matter stress are reduced drastically if not eliminated, when victims are shown the care, love and a sense of belonging.

Conclusion: It is evidently clear that a lot of pain could be minimised considerably when attention and care are given to those who need them and at the right time.

To make a headway, we must avoid stigmatisation in whatever form from.

This would build confidence in victims and all those related in the fight against this pandemic of human catastrophe. The psychological trauma alone builds an amount of life-threatening stress that quickens the pace to the grave. Information, education and communication(I.E.C) would help if applied well and timely.

PP 1.29.

Premarital Sex Towards Infertility and STD'S Infection

Smith C. Kwadaso-Kumasi, Ghana

Background: In Sub-Saharan Africa, Premarital sex is one of the major causes of infertility and some SDT'S. In Africa the proportion of young women having premarital sex has change very little, the average length of time between young women's onset of sexual activity and marriage is increasing. The gap is widening because women marrying later .In Ghana especially women started to have sex at younger ages in the past. WHY? Because it has become fun and privilege of showing love among themselves.

Method: Statistical analysis of the various clinics and interviews were conducted among doctors of some various clinics.

Results: Studies asked women age 13 -25 whether they have ever had sex. A question also asked whether they have been sexually active for about a month.

The result shows that about 80% of women having INFERTILITY and STD'S is caused by premarital sex and about 65% of HIV/AIDS and Cervical Cancer cases reported is also caused by premarital sex. Survey reported by John Hopkins University shows that Senegal condoms use increase from 15%-29% among unmarried sexually active adolescent women and from 7% -41% among such women ages from 20-24 between 1992-2000 has lead to this.

Conclusion: If there has been no proper care or new information implementing putting into place then we cannot avoid this catastrophe.

PP 1.30.**A Bridge of HIV Transmission Between Injection Drug Users and General Population in Ukraine**

Kyrychenko PD, Vlasova N. Vinnitsa Pirogov National Medical University, International Charity Organization "STEPS", Vinnitsa branch (Vinnitsa, Ukraine)

Although, the injecting drug use among young people remains the predominant mode of HIV transmission in Ukraine, the number of persons infected by heterosexual mode is steadily increasing. New diagnoses of HIV in persons infected through sexual intercourse accounted for about 35% of all new cases reported in 2003 - up from 15.3% in 1998. Therefore, the urgent issue today is developing preventive programs aimed at the groups of population that can easily spread the virus outside the injection drug users' (IDUs) cohort. In our study we investigated if female street commercial sex workers (FCSWs) might be one of such groups.

The data were collected in Vinnitsa, Ukraine. Our research team carried out interviewing among street female commercial sex workers. The questionnaires were designed to elicit demographic data, information about drug use practice and sexual behaviour leading to an increased risk of HIV. Altogether 70 female FCSWs were involved into the study. About 46% of the study subjects were IDUs. Among them 24.7% confessed to receive syringe sharing and 32.6% declared that they gave their used syringes to others. In addition, 34.3% inject narcotics in a group and 57.8% require assistance injecting. Only 64.8% reported using condoms during the last sexual contact and about 50% reported consistent condom use with clients. Reasons for occasionally not using condoms were: refusal by the client (reported by 55.3% of sex workers), permanent client (42.1%), and higher payment from a client (39.5%). Being on the margin of society, the ability of commercial sex workers to negotiate safer working conditions is limited. Moreover, their financial position can make them vulnerable to customers willing to pay more money for unprotected sex and other high-risk practices. About 68.3% of street FCSWs had injection drug users among their clients. About 42.1% of the respondents had an injection drug user as a regular partner. At the same time, solely 5.3% of the women reported consistent condom use with a regular partner. About 36.8% confessed to having injection drug users among casual partners while only 18% use condoms with them. In addition, the fact that 65.5% of the interviewees use narcotics before, at least, every second sexual contact, is undoubtedly alarming as well.

Street female commercial sex workers using injection narcotics, widely practicing syringe sharing and needing assistance injection, having IDUs among their clients and permanent partners and not using condoms with them consistently might be considered to be an HIV bridge between injection drug users and general population in Vinnitsa, Ukraine.

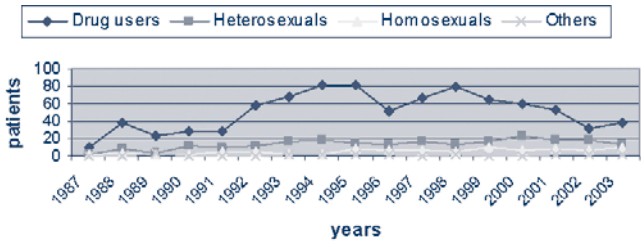
PP 1.31.
Trends in HIV Risk Behaviors in Castellon, Spain

Roca B, Ventura JM, Tornador N, Bahamonde D. Hospital General of Castellon, Spain

Background and Objective: Data are limited about the evolution of the relevance of the different HIV risk factors. We describe the behaviors associated with HIV transmission in the province of Castellón, Spain, and their change over time.

Methods: The medical charts of all 1240 HIV-infected patients attended at the outpatient clinic of the Hospital General of Castellón from March 1998 to December 2003 were reviewed.

Results: Sex, age, and HIV risk behavior were available from 1197 patients; 874 (73 %) were male and 323 (27 %) female; the overall mean of age when they attended the clinic for the first time was 32.8 ± 6.1 years. No significant differences were found in the percentage of gender or the mean of age among the different years. Figure shows the evolution of HIV risk factors. A clear descent in drug user transmission in the last few years was observed, although differences were not significant.



Conclusions: Since the beginning of the HIV epidemic, intravenous drug use has been the main way of HIV spread in Castellon, Spain, although the importance of this risk behavior has declined in the last years. Transmission via homosexual practices has been uncommon all the time.

PP 1.32.**Multi Drug Resistant Tuberculosis (MDR-TB) and Public Health Policy**

Atre SR. The Foundation for Research in Community Health, Pune, India

Despite enormous technical advances in medical science, even after 120 years of the discovery of germ, tuberculosis remained one of the major causes of death in the world. Furthermore, in recent years multi drug resistant tuberculosis (MDR-TB) is emerging as a possible threat to global TB control efforts. It is a challenge not only from public health point of view but also in the context of global economy. Biomedical accounts are insufficient to understand the dynamics of tuberculosis and emerging drug resistance. Hence understanding of the underlying social inequalities, which play pathogenic role in causing TB, is equally essential.

Both laboratory-based and social science research methods need to be integrated for effective TB control. Laboratory-based methods (such as molecular fingerprinting etc.) would provide the biomedical understanding, whereas social science methods (such as qualitative and quantitative) would inform the role of behavioral and social factors and possibly how these lead to biomedical outcomes. This concept paper would attempt to provide a holistic approach of anthropology encompassing the role of socio cultural factors such as poverty, homelessness, gender, and financial problems in taking treatment and social stigma, which prompt the patient to interrupt the treatment or shop around. Similarly, it explains the role of biomedical factors such as use of antimicrobials, negligence of people in health system, Nosocomial transmissions and spontaneous mutations in bacteria leading to drug resistance. This would be applicable for other infectious conditions, where the problem of drug resistance is emerging.

PP 1.33.

Reducing and preventing HIV/AIDS and other STIs incidence and prevalence among cross-cultural groups in South Florida, Haiti and Jamaica: A Tri National Project.

Delva F, Fanfan MF. Florida International University, Florida Memorial College, Miami, University of South Florida, Tampa, Florida, USA

Problem:

In South Florida, Jamaica, and Haiti, the incidence and prevalence of Human Immune Virus and the Acquired Immune Deficiency Syndrome (HIV/AIDS) are at least respectively 25 percent (%) higher among cross-cultural groups than among at risk people of the general population. The targeted group in South Florida, Jamaica, and Haiti include African American women (34,645), Haitian women (31,000), Jamaican women (27,000), Cuban women (39,000), Mexican women (18,990), and other Latina (80,000) from a total population of 3,789,097 people (Census Bureau, 2000). In Jamaica and Haiti the selected population and location are mostly metropolitan areas of Kingston, Saint Thomas and in Port-au-Prince areas of Kosovo, La Saline and others. Consequently, all participants were considered as at risk of HIV/AIDS, Sexually Transmitted Infections (STI) and even Tuberculosis. In the United States of America (USA) at least 62% of all participants in this program belong to the cross-cultural groups instead of minority. Among the cross cultural groups the incidence of HIV/AIDS is at least 200 infected people per million, while it is 400 per million in Haiti. In Jamaica, the total number of persons reported with AIDS since the start of the pandemic was 7,543 (4,514 or 59.8% males, 3,029 or 40.2% females) as of June 2003. The number of children reported with the pandemic is 22 during that same period. As of April 2004, there are 22,600 persons living with HIV/AIDS in the Island of Jamaica. It is the second leading cause of death in children aged 1-4 years. At least 33% of persons infected people have a history of STI and 18% were recently treated for STIs (Ministry of Health, 2003).

Methodology:

In November of 2002, an interdisciplinary team consisting of Internist, Public Health practitioner, and a Infectious Diseases Specialists started the program with a study group of 1000 randomly selected from a targeted population of 3,789 high risk determined by behavior and other data. All participants reside in South Florida Tri County: West Palm Beach, Broward and Dade, and originating or residing in Jamaica, and Haiti. They were also all of the low income /cross-cultural groups. The specific aims of the program were (1) to improve health status; (2) to reduce incidence and prevalence of HIV/AIDS, STIs and TB; (3) Improve the quality of life of HIV infected people considering the AIDS Spectrum. The process objectives were: (1) to provide a research oriented medical profile capable of facilitating the interrelation of health education, health promotion, nutritional status measurement and curative/preventive action; (2) to provide culturally competent health communications for the at risk people consisting of individual (ILI) and group level of intervention (GLI); (3) Social marketing (Community outreach) for community-based medical interventions i.e., diagnostic and treatment of diseases related to HIV/AIDS, STIs and TB; (4) Capacity building for social support (Public Information i.e., radio, television and newspapers). The outcome objectives were: (1) At the end of one year, the incidence and prevalence of diseases related to HIV/AIDS will be reduced by 5% with an accumulative reduction rate of 25% in five years; (2) At the end of one year, the incidence and prevalence of STIs and TB will be reduced by 15% with an accumulative reduction rate of 75% in five years; (3) At the end of one year, the health status of the whole population study and target group will be improved by 5% with an accumulative improvement rate of 25% in five years. Efforts and impact will be evaluated at the end of year 2004.

Results in the Tri Countries:

The total number of people tested for HIV in the US is 607 in two years, in Haiti, 28,416 and 7,900 in Jamaica. The number of persons tested for Syphilis in Haiti is 23,769; in the US, the number is 267 and 16,890 in Jamaica. In the US all cases were treated as of April 2004, in Haiti, the number treated is 980 and in Jamaica the number treated for Syphilis is 657. The number of people treated

for STIs in Haiti is 3,450 and 879 in Jamaica and 56 in 677 in the US. In Haiti, the number of people screened for TB is 2,989 and in Jamaica it is 1,709. Only 7 persons were registered at the Halley Hospital in Lantana, Florida. In Haiti the number of pregnant women tested for HIV is 2,567 and about 225 women are currently being treated.

Impact and Evaluation:

The impact of this two year program is multi factorial: as of March 2004, at least 75 % of the participants in this program increased their compliance to medications, nutritional supplements and regular exercise by 80%. The monitoring and regular evaluation reveals an increased in knowledge and attitude among all participants. The evaluator used a longitudinal study with a comparison group over time; and internal and external validity were respectively confirmed. Hypothesis testing will be performed for establishing overall statistical significance by using a p value of <0.001 with an $\alpha=0.05$ with a Confidence Interval (CI) of 95%.

Implications:

South Florida in year 2004 remains one of the most diversified geographical area with a high multicultural population in the United States, yet in March of the current year, such demographical division still prevails for disparities in Health care, health status indicators and risk factors (as pre-cited). The disparities are based on income, race and ethnicity. This program responds to the criteria elaborated in Healthy People 2010; it has improved access to health care, health promotion information and education, and AIDS counseling and testing or the participants and many members of the targeted population. It has helped prevent related diseases; and has strengthened the link between behavior modification, medication compliance, nutrition and physical activity through health education and promotion.

Institutions or agencies where the Action Research was performed:

Cultural Health Exchange of Latin Americans United Inc., with the collaboration of many agencies including but not limited to: North Broward Hospital District, Jackson Memorial Hospital, University of Miami-Behavioral Department and Haitian Physicians Association (AMHE) Clinical activities, and Nova Southeastern University.

PP 1.34.

Factors Associated with Continuation of High-risk Behaviour by HIV-positive Injection Drug Users

Kyrychenko P. Vinnitsa Pirogov National Medical University, Vinnitsa, Ukraine

As HIV-positive injection drug users represent a major vector of HIV transmission, not only to other drug users but also to their non-drug-using sexual partners, and potentially to their offspring, there is an urgent need to identify antecedents of both drug- and sex-related HIV-risk behaviour in this cohort to facilitate the development of effective risk-reduction interventions.

Interviewing was conducted among HIV-positive injection drug users (IDUs), who visited outpatient clinics in Vinnitsa, Ukraine, during 2003. Altogether 74 persons (48 men and 26 women) were recruited in the study. The relationship between high-risk behaviour (sharing injection paraphernalia and having sex without condoms) and possible predictor variables was first examined in a bivariate analysis, and then via multiple logistic regression. Outcomes were measured using Odds Ratio (OR) with its 95% Confidential Intervals (CI).

HIV-positive IDUs, who continue high-risk behaviour, were more likely to be female (OR 2.2; 95% CI 1.2-4.3), have been younger (OR 2.1; 95% CI 1.3-4.5), had sex with a casual partner (OR 3.1; 95% CI 1.9-7.4), injected drugs in a group (OR 2.8; 95% CI 1.6-5.3), had lesser duration of drug use (OR 3.6; 95% CI 2.0-7.3), and needed assistance injection (OR 2.7; 95% CI 1.5-5.4). They were less likely to live or inject at their own home (OR 0.58; 95% CI 0.21-0.76), been married (OR 0.64; 95% CI 0.32-0.88) or had a permanent partner (OR 0.32; 95% CI 0.17-0.82). In a final logistic model, correlates of HIV-risk behaviour continuation included gender (OR 2.6; 95% CI 1.2-5.7), injecting outside one's home (OR 2.3; 95% CI 1.2-7.6), and needing assistance injection (OR 2.1; 95% CI 1.3-3.8). Individuals with mentioned above predictors might be ones, not only spreading HIV among injection drug users, but also passing the virus to the general population.

Protecting of HIV-negative persons is not enough to stop HIV epidemic. Motivating HIV-positive people to reducing their risk behaviour is urgent today as well. Hence, young female HIV-positive injection drug users, who have sex with casual partners, inject drugs in a group, need assistance injection, inject outside their home, and are not married, need a special emphasis in HIV preventive programs in Vinnitsa region of Ukraine.

PP 1.35.**Lost Opportunities of Detection of HIV Infection during Pregnancy in Brazil**

Szwarcwald CL. Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Introduction: Although ARV treatment is universally available in Brazil, and improvements have been noticed lately, mother-to-child HIV transmission remains in unsatisfactory levels. In this study, lost opportunities of detection of HIV infection during pregnancy have been examined. **Methods:** The effective coverage of HIV testing during pregnancy was defined as the proportion of women that had prenatal care (at least one consultation), offering of HIV testing during pregnancy and knowledge of the result before delivery. The data source was the World Health Survey carried out in Brazil, in year 2003. A sample of 252 women pregnant in years 2001 and 2002 was analyzed. The coverage was estimated by statistical procedures, taking into account the sampling design of the survey. Inequalities of the effective coverage were analyzed by: number of assets; educational level of the mother; public/private sector. **Results:** The effective coverage of HIV testing during pregnancy was estimated as 56.7%. Notable socioeconomic inequalities were evidenced by comparison between women with incomplete education (42.5%) and women with complete secondary instruction (78.6%). The lowest coverage (34%) was found among the 99 poorest women (with less than 4 assets). For the 175 women with prenatal care at the public sector, HIV testing was offered for only 110 women (62.8%). From these, 107 agreed to be tested, but only 92 (52.6) received the test result before delivery. **Discussion:** The findings indicate pronounced bottlenecks in the effective coverage of HIV testing during pregnancy, as steeper as the worst is the socioeconomic status. The high proportion of lost opportunities of HIV detection during pregnancy, mainly in the public sector, establishes the need of urgent actions. The findings indicate that to have universal ARV treatment is not sufficient. One of the greatest challenges to be faced is to ensure that actions undertaken to improve HIV detection during pregnancy succeed in having a comprehensive impact, particularly among those women that are most difficult to access with preventive measures.

PP 1.36.

Prise en Charge des Enfants Orphelins du SIDA

Jacquie Militoni. Santé et Développement Communautaire, RDC

La République démocratique du Congo traverse une période de crise aggravée par les conflits armés dont les conséquences néfastes touchent les populations vulnérables, surtout les enfants rendus orphelins par le VIH/SIDA.

Ces enfants vivent dans les conditions extrêmement difficiles et tombent dans la marginalisation. Ils se retrouvent dans les rues, marchés, ports, aéroports, gares, dans les forces armées... Où qu'ils se trouvent, ils sont confrontés à la violence, à la malnutrition et sans protection. Ils sont sans accès aux soins de santé, à l'éducation de base, à la formation scolaire et professionnelle.

Une intervention planifiée avec l'appui du PNUD/PNLS a été exécutée en faveur de 600 orphelins du Sida dans les quartiers les plus mouvementés de la ville de Kinshasa notamment Matonge et Yolo et ayant comme résultats :

- 60 volontaires formés comme des assistants sociaux.
- 475 orphelins réinsérés dans des familles d'accueil en 2001
- 600 orphelins scolarisés, nourris et habillés en 2002 et 2003
- 220 familles d'accueil formées en activités génératrices de revenus

La prise en charge de ces orphelins n'est pas facile à réaliser compte tenu de difficultés ci-après :

- Moyens d'intervention limités;
- Réinsertion difficile dans les familles à cause du phénomène " enfants dits sorcier " et de la pauvreté des ces familles;
- Implication difficile des familles d'accueil dans la prise en charge des ces enfants.

PP 1.37.**Infant Feeding In The Context Of HIV/AIDS: A Call To Action**

Liles C, Tompson M. AnotherLook, Evanston, Illinois, USA

AnotherLook is issuing a Call to Action to ensure optimization of maternal/infant health in terms of morbidity and mortality in research, policy, and practice as it relates to infant feeding in the context of HIV/AIDS. Breastfeeding is a critical element in optimal maternal/child health. Feeding infants when the mother is HIV positive has become an issue of great concern. Current policy (1), research (2) and practice (3) which prioritize reduction of mother-to-child-transmission while neglecting the impact on morbidity and mortality may not only be misleading but may inadvertently setback gains in public health related to breastfeeding promotion. While acknowledging that HIV may be transmitted through breastfeeding and that there is an urgent need for feeding guidelines, and recognizing that there is no clear published scientific proof that infants born to mothers who are HIV positive would be healthier and/or less likely to die if they were not breastfed, AnotherLook has issued this call to action. It is time for peer reviewed, unbiased and ethical research which will provide scientific evidence of optimal infant feeding practices leading to lowest morbidity and mortality based on careful study follow-up. This call is aimed at policy makers, researchers, health workers and funding bodies, locally and globally to return to basic scientific, medical, public health, and fiduciary principles in responding to this issue. It is time for ensuring accountability, responding rather than reacting to fear, raising critical questions, stimulating needed research and evaluating information about infant feeding and HIV/AIDS. It is time for action.

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3. McIntyre J, Gray, G. What can we do to reduce mother to child transmission of HIV? BMJ 2002 Jan 26; 324: 218-21.

PP 1.38.

Surveillance study of selected sexually and blood transmitted infections in HIV-negative vs. HIV-positive pregnant women and their newborns in SR.

Stanekova D, Adamcakova J, Kopilcova T, Kotuliak J, Vaculikova E, Habekova M, Mokras M.
Slovak Health University, Bratislava, Slovakia

Objective: Prevalence of infections caused by CMV, HCV, HBV and Treponema pallidum was investigated in groups of HIV-negative and HIV-positive pregnant women and newborns born to HIV-infected mothers.

Methods: 90 HIV-negative and 6 HIV-positive pregnant women and 6 HIV-negative newborns of HIV-infected mothers were investigated in 2003. For the determination of antibodies to HCV, CMV, T. pallidum as well detection of HBsAg MONOLISA® anti-HCV PLUS Version 2 /BIO-RAD/, ETI-CYTOK -G PLUS /DiaSorin/, ETI-CYTOK-M reverse PLUS (DiaSorin), TPHA 200 /Newmarket Laboratories Ltd/ and Murex HBsAg Version 3 (ABBOTT) tests were used, respectively.

Results: In the group of HIV-negative pregnant women HbsAg, CMV IgG and antibodies to T. pallidum were found in 4.44% (4/90), 80.0% (72/90) and 1.17% (1/85), respectively. Neither HCV Ab nor CMV IgG were observed in this group. The highest rate of selected co-infections was detected in the group of HIV- positive women. In the group of HIV-positive women HbsAg, HCV Ab and CMV IgG detected in 16,6% (1/6), 33,3% (1/3) and 100% (6/6) cases, respectively. Neither antibodies to T. pallidum nor IgG CMV were found in this group.

In the group of babies born to HIV-infected mothers HCV Ab transmission was confirmed in the newborn whose mother was found HCV IgG positive. Despite of the fact that all mothers had IgG antibodies to CMV, acute CMV infection of newborns was not confirmed after delivery. HBsAg was not detected in child born to HbsAb positive mother thanks child's vaccination early after delivery.

Discussion: High prevalence of selected sexually and blood transmitted infection was observed in the group of HIV-positive pregnant women compared to HIV-negative one. Based on these findings increased attention should be paid on the prophylaxis reducing mother-to-child HIV and other STI transmission

PP 1.39. Mobilisation des Femmes Infectées et Affectées par le VIH/SIDA pour une Large Réponse à l'Epidémie

Outiama P. Dpt Santé, PVVS, Bangui, RCA

INTRODUCTION:

vu l'ampleur de l'épidémie en Centrafrique, chaque groupe doit se mobiliser; les femmes constituent un exemple patent pour contribuer à la réduction de la propagation à travers la présente expérience.

OBJECTIFS:

- Impliquer les femmes dans la réponse communautaire;
- Développer l'esprit de partenariat dans la prise en charge des orphelins et les malades du SIDA;
- Eduquer les jeunes pour se protéger contre l'infection à VIH/SIDA.

METHODOLOGIE:

- Formation des pairs éducatrices et des femmes affectées et infectées par le VIH/SIDA;
- Création des activités génératrices de revenus;
- Organisation des compagnes de sensibilisation de proximité avec distribution de bons de dépistage gratuit.

RESULTAT:

- 60 femmes formées pour le counselling et la prise en charge;
- Participation au pré et post test dans les unités de santé;
- 120 enfants recensés dont 60% ont été pris en charge (nutrition et santé)
- Des activités génératrices de revenus ont été créées dans sept (7) quartier de la capitale;
- 2 séances de sensibilisation par semaine organisées par les pairs éducatrices.

CONCLUSION: La majorité des femmes en Centrafrique ont pris conscience de leur rôle en tant que mère au foyer pour participer à la lutte efficace contre le SIDA, ces actions ont été une réussite dans la capitale; l'idéal serait d'élargir cet exemple à l'intérieur du pays.

PP 1.40.

Public health surveillance of sexual exposure to HIV in the French Armed Forces in 2002

Michel R, Ollivier L, Aiesi F, Meynard JB, Boutin JP. IMTSSA, Marseille, France

Sexual intercourses are at risk of HIV transmission, mainly on duty areas for French soldiers. Since January 2000, a public health surveillance has been set up in the French Forces. The case definition is "unprotected intercourse, condom breakage or slippage declared within 48 hours after exposure". Cases are followed for a 6 month period after the exposure. In 2002, 554 cases were notified. Most of them (321 cases) occurred on duty areas, areas of high HIV prevalence. The proportion of breakage or slippage declared was 90.1%. In 71.6% (366/511) a commercial sex worker was visited. Eight out of 30 sex workers tested were HIV seropositive. A post exposure prophylaxis (PEP) was proposed and accepted in 82.5% (457/554). No HIV or HCV transmission was notified during the following. At the end of 2003, the French Health General Direction decided to stop the surveillance of sexual exposure to HIV. But the French Forces Medical Services decided to maintain this indirect measure of sexual risk behaviour.

PP 1.41.**Guaranteed Education on Safe Sex and HIV Related Infections for Cameroonians in Relation to Blood Donation**

Itoe Francis Ebongue

President/National Coordinator

Natural Initiative for Voluntary Blood Donors "NIVBLODON"

BP. 112 Buea, Fako Division

South West Province - Republic of Cameroon

ABSTRACT: The urgent need for intensive education and training to the sexual active population in Cameroon is the order of the moment by all patriotic health care providers. The objectives of this work will be: To witness the dropping degree of ignorance to gross awareness and practically putting in action an individual behavioral change in sex and HIV related infections, to create an individual network for blood donors and prospective donors for voluntary participation in saving lives and also to educate them on the risk of contracting HIV and related infections in blood donation process. At the end of this program, we expect every individual to adopt a decisive strategy to keep away from unsafe sex, encourage Blood Donation and to prevent other infectious diseases related to HIV/AIDS.

DESCRIPTION: Following the rapid spread of HIV and unsafe sex related infections, this project is designed to mobilize, train and individually employ the target population (sexual active group) to know what they ought to know and do in their sex eager lives. This will therefore draw participants from all the six Divisions in the South West Province of Cameroon to spread the education and also to train others on how to run away from the risk of contracting HIV and related infections. Following a research carried out some few months ago about the eradication of HIV amongst us, there are all indications that this project will do much to change the situation. Thanks to the efforts contributed by religious groups for this program.

PP 1.42.

Prevalence of HCV Specific antibody, RNA and genotypes among HIV infected Iraqi haemophiliacs

Prof. Al-Kubaisy W. A. (MBChB,Ph.D)* AL-Naib K.T.(B.Sc.,Ph.D)** and Habib M.A.(MBChB,Ph.D)**

*Al-Nahrain University/ Collage of Medicine, department of community medicine

**Al-Nahrain University/ Collage of Medicine, department of Microbiology

Aim: To estimate the seroprevalence of HCV infection among HIV infected haemophilic and to demonstrate the most prevalent HCV genotype among them.

Methods: A sample of 47 HIV infected haemophilic patients were screened for anti-HCV antibodies using a third generation enzyme immunoassay. Positive results were then confirmed by third generation immunoblot assay. By performing polymerase chain reaction (PCR) and DNA enzyme immunoassay (DEIA), HCV-RNA was detected with subsequent genotyping.

Results: The seroprevalence of anti-HCV antibodies was 65.96%. Out of 31 HCV/HIV coinfecting patients, 21 (67.7%) were lacking history of blood transfusion. Four HCV genotypes were detected (1a, 1b, 3a and mixed 3a & 4) in 15.38%, 61.53%, 15.38% and 7.69% respectively.

Key words: Haemophilic, HCV, HIV.

Conclusion: HCV-1b was found to be the most frequent detected genotype among HCV positive Iraqi haemophilics coinfecting with HIV. Moreover, contaminated factor VIII sound to be responsible for disease acquisition. More details are interpreted in the text.

PP 1.43. HIV/AIDS, STI Prevention And Sex Education In Nepalese Schools/Colleges Youths

Gautam R, Koirala M. BP Memorial Health Foundation, New Baneshwor, Kathmandu, Nepal

Purpose: To determine impact of Knowledge Attitude and Behavior regarding, sexual and ARH, HIV/AIDS and STD, peer education activities among school/college students of Kathmandu and Kaski Districts of Nepal.

Methods: The evaluation was done comparing results of final survey with baseline survey. In baseline and final survey 792 (7.4%) and 596 (7.1%) students from 16 selected schools and 15 colleges were selected through stratified random sampling for participation in the survey and completed the questionnaire (14-22 years) participated respectively.

Results: The higher level of knowledge increased 71.9 to 93.8% & prevention 42.4 to 94.3% whereas misconception reduced (mosquito bite 37 to 16%. Knowledge about reproductive physiology increased moderately e.g. safe period 23-59%, sex determination 31.5 to 66%, organ where baby develops 54 to 89%. Regarding risk behavior premarital sex 11 to 11.7 approval rate 34 to 31% & mean age of first sex 15.5 to 16.3%. Similarly those who have seen condom increased 64 to 88% & its use 77 to 91% while having sex & sex against their will changed 27.3 to 24%. Drug use (currently using) among college male changed from overall-37 to 25% & in injecting drug 10.4 to 0.8%. Most of the students favor of sex education at schools 86.4%. 27.4% said it is okay to have pre-marital sex. Almost half 44% regarded friends to be the most informative source of knowledge about sex 25.6% said they have currently love affair out of which 14.7% reported sexual relation who considered peer as main source of information 44 to 65%.

Conclusions: The peer education has brought positive changes in all aspects of knowledge, attitude and behavior though changes are less dramatic where baseline was high. Students have identified peer-educators as most significant source of information and very high proportion of student knew about their activity. It seems that peer education has significant influence among friends to behave 'safer' way and reduce drug abuse.

PP 1.44.

The women's antenatal care initiative for reduction of HIV mother-to-child transmission in Colombia - The Mother & Child Project - (project funded by the European Commission)

García Bernal R, Arenas Granada CD, Prieto Alvarado FP, Rincón Ramírez JA, Vargas LE, Ramírez Ramírez CM. UNAIDS, Bogotá, Colombia

Background: This project, based on previous pilot projects conducted between years 2000 and 2002 (approx. 16,000 women tested), is focused on the poorest female population, and based on a intervention integrated to the antenatal care programs. Main project objectives include recognition by Colombian women of the importance of knowing their status for HIV infection; to offer free HIV testing as part of the antenatal care; to provide adequate health care to women infected including ARV treatment; to provide psychosocial support to infected women and their families; to obtain the commitment from health entities; and to implement a national public health policy for reduction of MTCT. Methods: Project implementation started in April 2003, has included regional coordination and training activities; pre and post-test counseling; provision of psychosocial support and recommended ARV treatment options; production of a social marketing campaign; clinical management of infected women and newborns; caesarian delivery; counseling on nutrition and provision of breastmilk substitutes; and advocacy for permanent affiliation of HIV infected mothers and their newborns to the Health System. Results: Since April 2003, nearly 58,000 pregnant women were tested in 25 of the 32 country geographical departments. 154 women (0.3%) have been diagnosed as HIV infected and received ARV treatment (mainly ZDV+LAV), psychosocial support and lab monitoring. The 120 babies born received ARV treatment for six weeks, and replacement formula; and all born free of infection. The social marketing campaign "To your child, transmit only love" is being displayed nationwide, in TV and radio channels. Involvement of public and private health institutions was achieved. Sustainability of project activities was assured by public national and regional health authorities. Conclusion: Reduction of MTCT transmission is a highly effective intervention for preventing epidemic expansion in low prevalence countries not only for decreasing at the minimum level the incidence of pediatric infections, but also for promoting women's empowerment towards protective attitudinal and behavioral changes in their own sexual relationships.

PP 1.45.**Prevalence Of Drug-Resistant HIV Mutants In Recently Infected And Naïve Patients In Liguria, A North-Western Region of Italy**

Setti M, Bruzzzone B, Ventura A, Murdaca G, Frabetti M, Icardi G, Indiveri F. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa, Italy

Several studies showed that transmission of HIV strains resistant to antiretroviral drugs can occur. Although somehow discrepantly, those studies point out that HAART may be started in naïve patients infected with unrecognised resistant virus, leading to the risk not only of early failure, but also of increase of resistance, which hampers the choice of salvage protocols. The serious concern about this jeopardy has not yet led to a precise definition of the problem, nor to an accurate investigation of the phenomenon in distinct local settings or in the different HIV+ populations. In order to assess the prevalence of resistant viruses in our region in the various groups along the time, we sequenced all the detectable viruses prospectively from the newly infected individuals arrived to our laboratory from a clinical centre in Liguria, as well as all the viruses from HIV+ subjects from the same centre who had never yet been treated, prospectively or retrospectively in the oldest sample available. We searched for the presence of NRTI, NNRTI and PI resistance-associated mutations by mean of a TRUGENE-HIV1 genotyping test. In 7 samples out of the overall 98 enrolled patients (62 males and 36 females, 10 in 1999, 22 in 2000, 12 in 2001, 23 in 2002, 25 in 2003 and 6 in 2004) virus was undetectable or < 500 copies/ml. In 11 of the 91 valuable samples (12.1%) resistance-associated mutations were found: primary mutations for resistance to NRTI in 8 (8.8%), to NNRTI in 6 (6.6%) and to PI in 2 (2.2%). In 3 subjects (3.3%) the virus bore resistance to 2 classes of drugs. The mutations found were overall 30, in 13 sites: M184V (5), L41M, L210W, T215Y and K219Q (3), T69D (2), D67N, T215F and T215S (1); K103N (3) and K101Q (2); F53L and L90M (1). Their prevalence by year was: 0% in 1999, 9% in 2000, 8.3% in 2001, 4.3% in 2002, 20.8% in 2003 and 50% in the first 3 months of 2004. Moreover, a very high prevalence of polymorphisms (especially L63P) were observed. Finally, 6 wild type non-B clades (3 E, 2 F and 1 G) were also detected. In conclusion, the circulation of mutated strains in Liguria has been low, but is sensibly increasing in the last two years, approaching or even overcoming the values reported in studies in other western countries. The circulation of polymorphic strains, as well as of non-B clades, might have an impact on the onset of new mutations and on the clinical outcome, that will be evaluated in the future. The execution of resistance testing before starting HAART when the criteria are met seems to be recommendable in naïve patients in our region, especially in the most recently infected individuals.

PP 1.46.

Occupational Exposure To HIV, HBV And HCV Among S. Martino Hospital Health Care Workers (Genoa) In The Years 1989 To 2003

Setti M, Cardinale F, Riccio C, Sticchi C, Talassio G, Frabetti M, Icardi G, Bruzzone B. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa, Italy

-Setti M, Cardinale F, Riccio C, Sticchi C, Talassio G, Frabetti M, Icardi G, Bruzzone B. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa, Italy

The Genoa University Health Science Department is taking part in SIROH (Italian Study of HIV Occupational Risk) by systematically gathering, cataloguing, reviewing and analysing the professional injuries with a biological risk occurred in the S. Martino in Genoa. The aim of this research is to define the risk of occupational infections due to the exposure to haematic transmission pathogens (HIV, HBV and HCV). Since January 1989, our department has gathered the complaints by those health care workers (HCWs) who came in contact with HIV risk biological substances and, starting from 1992, the supervision has been broadened to include also HBV and HCV exposures. The information has been obtained through anonymously completed questionnaires, paying a particular attention to the birth-age and professional data, how such injuries have occurred and, if known, the serological condition of the source subject. Since January 1989 up to December 2003, 1921 professional accidents have been notified; 980 were complaints following exposure to known biologically contaminated substances (51 %): 126 cases to HIV, 753 to HCV, 142 to HBV, 26 to HIV +HCV, 4 to HIV + HBV, 8 to HIV+HBV+HCV and 23 to HBV+HCV. Out of all the reported injuries, 77 % were referable to cut wounds or needle-pricks or other sharps objects; 15 % were to be imputed to skin contamination and 8 % to mucosal contamination. Nurses were the professional category mainly involved (67 %); doctors (19 %) and other medical profiles (14 %) followed. A firm majority of injuries following venous and arterial blood withdrawal, intramuscular or hypodermic injections and intravenous therapy have been noted if compared to other penetrating actions done on the patient. Universal precautions at the very moment of the accident had been taken only in 70 % of the cases. As far as the site of the accident is concerned, noteworthy the prevalence of injuries happened in non-critical areas (patient rooms, corridors and ambulatories). Only 71 % of the involved medical operators had previously undergone active HBV prophylaxis and 98 % of non-immune subjects accepted post-exposure prophylaxis for such a virus (vaccine or immunoglobulin administration). No HIV and HBV infections occurred in the HCWs during the period of observation, whereas 3 cases of seroconversion to HCV+ were found. This research allowed us to identify the professional profiles who mainly get involved into occupational exposure, the kind of the most representative risks, the major ways of exposure and the inadequate application of the eyes and face protection devices. Moreover, it faced us with the necessity to improve personnel awareness about the utilization of the active prophylaxis against B viral hepatitis.

PP 1.47.

AIDS: Ethics in the Information

Silva HMS. University of Itaúna, Itaúna, Faculty of Formiga, Formiga , Faculty of Pará de Minas, Pará de Minas, Brazil

The unrest in relation with the proposed subject arises in parallel with the increase of the AIDS-epidemia in our country and the rest of the world; In the activity of teaching we perceive the difficulty of diffusion of secure information on the disease. Both teachers and pupils find themselves in the middle of a maelstrom of news, supposedly scientific, that indicate in directions not always within reason. In the mid-nineties a new actor appears in the spreading of knowledge on the disease: the Catholic Church. They affirm that the best way to contain the epidemic, using a preservative, wouldn't be effective. In the beginning we thought these words wouldn't find ears to hear them, due to the absurdness of their meaning and would not be sufficient because of the severeness of the situation. Unluckily there was a repercussion in our country. Influenced by the voice of the Vatican, priests, many of them popular within groups of adolescents and younger people, indoctrinated the population not to make a habit of using the preservative. By the end of the nineties it is visible that this information is widespread, inclusive amongst teachers, especially those of Science and Biology who use their authority to preach against the use of preservatives. Using arguments of a pseudo-scientific nature, which makes the situation highly delicate in potential, considering the influence those teachers have on society. This work aims at the discussion of this dreadful situation, as well as to propose alternatives that may diminish the negative impact being generated, going against the AIDS-prevention programmes and increasing the risk behavior. It is necessary to emphasize the relevance of this subject, as we can already see the consequences happening. Young students abandon their safe behavior, like using the preservative, as mentioned before, in the false understanding that this is the right attitude. We believe that this subject - spreading information on AIDS - is within the sphere of the interest of Bioethics because it deals with information on people's health and, fundamentally, is related to agents, teachers, upon whom society has instored the diffusion of knowledge. Finally it would be interesting to make the present situation more problematic for the purpose of analyzing the situation and to search for contributions for the various sectors that participate in the congress. The amplitude of the question and its urgency, considering the fact that it leads to risky behaviour and possibly to the prejudice of the prevention campaigns, as well as cases of contamination.

PP 1.48.

Knowledge, Perception And Acceptability Of Microbicides (KPA) Among Non-health Care Givers In Lagos, Nigeria

Smith SI, Agomo C, Idigbe EO. Nigerian Institute of Medical Research, Lagos, Nigeria

Introduction: Little or nothing is known about KPA of non-health care givers to microbicides as substances that help to inhibit or prevent transmission of HIV and other STI's depending on the type used. Although spermicides are available in pharmacies in Nigeria and not widely used microbicides are not yet introduced in Nigeria.

The study was aimed at KPA among non-health care givers as a means to help to educate those individuals that are at high risk of developing HIV/AIDS and other STI's on the importance of these microbicides.

Methods: Questionnaires on KPA of non-health care givers on microbicides in Lagos, were distributed randomly to non-health care givers working in the Private Establishments, Govt. Establishments and students.

Two hundred non-health care givers were enrolled in this study.

Results: The highest age groups interviewed were in the 20 - 29 and 40 - 49 age groups (33%). The least of the age group was 15 - 19 years (8%). Fifty-six point five of the respondents had tertiary education, while 37.5% had secondary education and those with primary school education were 6%. Fifty-six point five percent had heard about microbicides, while 43.5% did not hear.

When asked if they were willing to use the microbicides, 63% were and 37% were not willing. Out of those willing to use microbicides 59% believed that it could protect from HIV, while 41% did not believe. Those who had heard about microbicides heard mainly from friends 38%. Nineteen percent heard from internet, while 13% heard from

colleagues and from pamphlets. The few who believed it could protect from HIV preferred to administer them as gels (44%). Majority (58%) preferred to buy the microbicides from pharmacies. The use of the internet did not affect the age groups much. The 20 - 29 age groups were 8.5%, while the 40 - 49 age groups were 7%. The tertiary education, helped in enabling them to have heard about microbicides (35%), compared to 20% with secondary education and 2% with primary education.

Discussion: This KPA study highlights the need to educate non health care givers about microbicides particularly those of low level of education as they are most often the fastest source of HIV/AIDS spread.

PP 1.49. Lubricants Containing N-9 May Enhance Rectal Transmission of HIV and Other STI's

Phillips D, Sudol K, Taylor C, Guichard L, Elsen R, Maguire R. Population Council, 1230 York Avenue, New York, Ny 10021; Sexologist Sexual Health Project, Castro Street, San Francisco, CA 94114, USA

It has been shown that men who have sex with men seek lubricants that contain nonoxynol-9 (N-9) because they believe that N-9 may help to prevent infection by HIV. However, there is indirect evidence suggesting that N-9 may actually enhance infection. A clinical study was undertaken to determine whether N-9 causes sloughing of the rectal epithelium and if epithelium repair rapidly following application of N-9. Biopsies and rectal lavages were used to determine if application of the 2% N-9 product K-Y® Plus caused sloughing of the rectal epithelium. To ensure consistency and compliance all procedures for the study were carried out by a clinical investigator. Lavage and biopsy specimens were collected at 15 min and 2 hr post-rectal use of K-Y® Plus in addition to a later time point. Specimens were fixed in buffered glutaraldehyde and embedded in plastic and stained. Blinded slides were examined by light microscopy. Pronounced sloughing was observed in rectal lavage and biopsy specimens collected at 15 min post application of K-Y® Plus. Sloughing was not observed in specimens collected at 2 hrs or 8 hrs post application K-Y® Plus and appeared similar to baseline specimens. Since rectal epithelium protects target cells in the submucosa from HIV; we conclude that lubricants containing N-9 should be avoided during rectal sex.

PP 1.50.

HIV/AIDS As A Part Of Health Policy - Acceptance

Lakhani A, Saiyyad YA. Deepak Charitable Trust, Vadodara, India

Issues: Risk of HIV/AIDS among industrial workers has drawn recognition as a workplace issue, repercussions on production and productivity profitability. This, coupled with a high sero-positive rate, frequency of HRB, easy availability of CSW due to intense logistics activities, migratory labor in security vocations, poverty in surrounding villages and multi partner relationships not a social taboo in the backward castes have become a cause of concern for policy planners.

Description: In Deepak Charitable Trust's (DCT) intervention area, socio-economic and psychological consequences have made unions to realize the importance of checking the spread. Multi partner relationships exist indicating value crisis. HRB continue due to ignorance, poverty, and migratory labor thus accelerating infections. Efforts have been made with industries by forming policies to create a supportive work environment for existing HIV/AIDS workers as also to create a safe environment for all workers by proposing to install condom vending machines. Acceptances of policy, by the industries, have given a sigh of relief amongst HIV positive people and enhance the cordiality in industrial harmony.

Lessons learned: Acceptance and implementation of policy is easier if the CEO is enlightened and cordial relations between the union and management. Desirable to educate employees through company's training programs. Small industries agree to spread awareness through leaflets, brochures, and exhibitions. Industry associations' support may elicit wider positive response.

Recommendations: Support from the government agencies may result in to expanded response from small industries. Cheap lab testing facilities should be made available in the industrial vicinity. Condom Vending Machines should be installed in factories. ARV drugs and treatment of the opportunistic infections at subsidized price would positively help the crusade against the dreadful disease.

PP 1.51. HIV/AIDS & Women's Economic Empowerment

Lakhani A. Deepak Charitable Trust, Vadodara, India

Issues: India's infection rate in the pandemic is worrisome as it translates to 3.7 million cases-more than half of all cases in Asia. Also, women account for nearly 17 million of the 36 million infected persons worldwide. Sexual abuse and their inability to negotiate safe sex have exposed women to the same.

Description: Currently, DCT's work in HIV/AIDS is in Nandesari village and the surrounding villages (20 kms from the city). This community is typically conservative with several restrictions imposed on women and subjugation of women is at its fore. DCT began its intervention in the field with the Partnership for Sexual Health (SHP) project funded by the UNAIDS. The interventions focused on identifying the high risk behavior cases (HRB) in the region and counsel them for behavior change and treatment with a special focus on women's empowerment.

Lessons learned: The project showed some striking revelations with a high prevalence of multi-partner relationships among men as well as women, within the villages itself. The trend of multi-partner sex among village women were seen to stem from a strong economic need than a mere sexual satisfaction. This was particularly seen among single women for whom HRB was an income generating activity. Also, proximity to highway added to commercial sex workers' (CSW) activity enhancing HRB in this population.

Recommendations: Thus, the paper is an attempt to draw a parallel between women's economic need and HRB contributing to the risk of HIV/AIDS. The results presented are in tandem with one of the most pervasive message, which states that, "gender equality and women's empowerment are a pre-requisite to stemming the tide of the epidemic" (Declaration of Commitment). And thus one of the crucial vaccines stemming the spread of the disease today is women's economic empowerment.

PP 1.52.
HIV/AIDS Care And Support Program

Annapoorni TM, Roberts VA, MacDonald LC. BLOSSOM, Virudhunagar, India

BLOSSOM's HIV/AIDS Care and Support Programme has been running for the last three years. The services we provide are as follows:

- Home based care / treatment for people living with HIV/AIDS
- A 'Compassion Group' of male and female volunteers who provide support for HIV/AIDS victims
- A counselling service for people infected or affected by HIV/AIDS
- 'Edu-Clowns' - educating and awareness raising programme

It has been observed that, once infected with HIV, the sufferer becomes vulnerable to a multitude of diseases; tuberculosis, skin disorders and diarrhoea. As well as having to endure these illnesses, the victims suffer discrimination from their communities which is often reported to be worse to bear than the disease itself. To help alleviate their struggle we strive to educate the community, through our group of 'Edu-Clown' performers. Previous performances have included skits promoting the importance of healthy eating, the boiling of water in order to make it safe to drink, the importance of hygiene and education. Prior to the performance, the Edu-Clowns will visit the communities to identify high risk areas, in order to tailor the performances in accordance to the peoples' needs. The 'Edu-Clowns' also help to dispel common myths such as the belief that HIV/AIDS is transferred via mosquito bites, and other common misconceptions. Their comical performances are based upon 50% entertainment and 50% education. Afterwards, the 'Edu-Clowns' integrate with the audience, thus stimulating discussion. Information booths are also set-up to allow people to access more information at their leisure. Due to the unique, thought-provoking nature of the Edu-Clowns performances, the information they convey is enthusiastically received, and the audience are inspired to take action. Through trial and error, we have found this method of promotion to be the most beneficial, as it is accessible to people of all ages, religions and literacy levels. In the last year, the Edu-Clowns have given around 50 performances to audiences of up to 500 people in the Virudhunagar and Sivakasi blocks. As a direct result of these performances, more people have begun to turn to BLOSSOM, especially with regards to testing for HIV/AIDS.

Our results over the past year are as follows:

Beneficiaries	Number receiving help
People living with HIV/AIDS	284
Family affected by HIV/AIDS	357
Children infected with HIV/AIDS	24
Children affected with HIV/AIDS	335

It has been observed that the number of people living with HIV/AIDS who visit hospitals for treatment has reduced remarkably due to family members and the people themselves beginning to initiate their own care. Thus medical expenses are reduced, health status is improved, and psychological satisfaction is gained by all.

It can be concluded that although both the Care and Support programme and 'Edu-Clown' technique, are very successful, we cannot ensure the maximum number of people are being reached, due to the stigma that still surrounds the HIV/AIDS issue. However, BLOSSOM is striving to increase AIDS awareness amongst the future generation, and to ensure that those already affected receive a high standard of care and support.

PP 1.53.**Coinfection of Hepatitis B and Hepatitis C Virus among HIV Patients in Ho Chi Minh City Vietnam**

Vo TTN, Nguyen HC, Maynard M, Nguyen VN, Ngo TKC, Pham VH, Truong XL, Follezu JY. Tropical Medicine Hospital, Pasteur Institute in Ho Chi Minh city, Binh Trieu Hospital, Preventive Medicine Center, Ho Chi Minh, Vietnam; University of Paris VI, Paris, France

Objective: to identify seroprevalence of hepatitis B and C virus infection among HIV patients in Ho Chi Minh Vietnam.

Method: 187 HIV infected patients who participated a screening for a clinical trial of ARV treatment were tested for detecting anti-HBs, anti- HCV, CD4 cell counts, bilirubin total, SGOT and SGPT.

Results: 74.9% of study subjects were male. Mean of age was 19.4. HIV infection through injecting drug was predominant (65.6%). Mean of CD4 cell count was low (248 cells/mm³ ± 186). High prevalence of hepatitis C virus was found (59.7%). Prevalence of anti-HBs was 16.7%. And 12.3% of 187 patients was found sero-positive of both anti-HBs and anti-HCV. Mean of SGOT and SGPT were 48U/l±42 and 53 U/l ±74. Mean of CD4 cell counts, SGOT and SGPT were significantly different from HIV patients seronegative of anti-HBs and anti-HCV comparing to patients seropositive of anti-HBs or/and anti-HCV ($p < 0.00005$). There was no significant difference of Bilirubin total among these groups ($p > 0.05$).

Conclusion: High sero-positive prevalence of anti-HBs and anti-HCV among HIV patients from this study suggested that the choosing combined regimens of antiretroviral should be considered carefully in order to minimize adverse events and to prove quality of life as well for HIV patients.

PP 1.54.

Mentality of PLWH/A and Affected Families in the Slum-based Poorest of Poor Community

Swamy G, Bansode S. John Paul Slum Development Project, Pune, Indonesia

DESCRIPTION: John Paul Slum Development Project is secular voluntary organisation basically working for the well being of slum dwelling PLWHA in Pune-India for those who are socially-economically downtrodden and neglected by the community wherein prevalence and incidence rate is on hike day to day due to their ignorance and mentality towards the HIV/AIDS issue.

FINDINGS: While devoting ourselves in the Home-Based Health Care Service for PLWHA in slums of Yerawada one of the biggest slum in the Pune District. We find that these people are having no concern with global epidemic but they are worried of their daily lively hood. Majorities are aware that this infection kills person after a long period. But at the same time they are not aware that if the PLWHA is mal-nourished and not received proper treatment and care for the opportunistic infection, may die within a very short period of time. Thus is the mentality leading to rise the incidence of HIV infections and deaths in the slum-dwelling community. To overcome this problems we have started House to House STD/HIV/AIDS Awareness by the initiating another socio-eco development programme which is the immediate concern and need for their benefit and have succeeded in moulding the slum-dwelling PLWHA.

CONCULUSING: After, all these effort taken we came to the conclusion that NGO can never enter in the HIV/AIDS Awareness programme and Home-Based Care Service in the slum community directly, unless it is having another socio-eco development programme along with it which will be the immediate need and concern of the community. And through such programmes we can avail the opportunity to strive hard to have Behavior Change in Slum dwelling PLWHA's daily routine life towards HIV/AIDS issues and can put control over the spread.

PP 1.55.**Demographics of HIV Patients Referred for Initial Visits to a NYC Clinic**

Jin S. Suh, Kinga Chieloszyk, Robert Warford, Phyllis Ristau, Victoria Sharp, New York, USA

BACKGROUND: The objective of this study was to assess the changing demographics and clinical characteristics of HIV patients presenting for initial evaluations to a multi-disciplinary HIV Clinic in New York City.

METHODS: A retrospective chart review of adult HIV patients who had initial visits between January-October 1998 compared to those who presented in January-October 2002.

RESULTS: Total of 521 charts were reviewed, 106 cases were excluded in the final analysis due to incomplete data and/or patients lost to follow-up.

	1998 (n=179)	2002 (n=236)
male/female ratio	67/33	71/29
race:		
African-American	56	52
Hispanic	33	35
Caucasian	11	13
median age:	45	43
primary risk factors:		
heterosexual	47	43
MSM	31	30
parenteral	22	27
median CD4+:	499	414
median viral load (bDNA):	39,565 (n=112)	88,821 (n=203)
opportunistic infection hx:	13	22
substance abuse hx:	35	44
mental health hx:	12	18
newly diagnosed (<6 months):	8%	5%
on antiretrovirals in the past:	59%	70%
on ARV's at initial visit:	15%	33%

CONCLUSIONS: The overall demography of HIV patients presenting for initial evaluations to this New York City clinic has not changed significantly since the beginning of the HAART era (1998). Majority of patients reflects the psycho-socioeconomic characteristics of the community in which this clinic serves. Preliminary data do suggest however, that most patients presenting for initial visits have had inconsistent access to primary HIV care (i.e., frequent emergency room visits, hospitalizations). Compared to 1998, trends reveal that recent pts have higher presenting viral loads, lower CD4+; and increased likelihood to have opportunistic infection, substance abuse and mental health histories. Also notable was that a significant number of patients had previously been antiretroviral regimens, but alarmingly, most had discontinued HIV medications due to multifactorial causes. These factors need to be further studied so that more effective strategies can be identified to improve continuity of primary care for HIV patients.

PP 1.56.**Homosexuality and HIV/AIDS in Kathmandu, Nepal**

Pkhakadze G. University of Madras, Department of Anthropology, Chennai, Nepal

Background: No study has been done in Nepal regarding the MSM community needs, behavioral patterns, its vulnerability to HIV/AIDS/STIs, and on the accessibility of health services to MSM. The public in Nepal believe that homosexuality does not exist. However casual sex between men happens and a limited gay community exists in Kathmandu.

Methodology: The methodology was cross-sectional with a detailed questionnaire for 110 respondents aged between 18-49 years and 5 group discussions, 4 case studies, examination for *Neisseria gonorrhoea*, and blood testing of 40 participants for VDRL, HBV, and HIV1/HIV2 rapid tests. The duration of the study was 120 days.

Results: Risk behavior among MSM community in Kathmandu is high and condom usage is low. The study showed that syphilis, HBV, HIV infections are still at a low level among the studied population. Access to health services, particularly to STD clinics, is constrained because of the stigma related to homosexuality.

Conclusion: An adequate MSM-only health facility is needed where MSM would be able to get an increased awareness about ways of transmission in order to reduce their vulnerability to the HIV/AIDS.

PP 2.1.**The Core Protein of Hepatitis C Virus Is a Potent RNA Chaperone Promoting Dimerization of the Viral Positive-Strand RNA**

Ivanyi-Nagy R, Cristofari G, Gabus C, Boulant S, Lavergne JP, Penin F, Darlix JL.
LaboRetro, INSERM U412, ENS de Lyon, IBCP CNRS, Lyon, France

Hepatitis C virus (HCV) is an enveloped virus with a positive-sense, single-stranded RNA genome encoding a ~ 3000 amino acid polyprotein that is processed to generate ten viral structural and non-structural proteins. The structural Core protein of HCV is a small, highly basic RNA-binding protein that is thought to coat the genome in the viral particle. Besides its structural role, the Core interferes with numerous host cell functions and contributes to the aetiology of HCV-induced liver disease by interacting with a diverse set of cellular proteins. Retroviruses are also enveloped viruses, containing a dimeric, positive-sense RNA genome that is extensively coated by several hundred molecules of nucleocapsid (NC) protein. In addition, retroviral NC proteins possess nucleic acid chaperone properties that play critical roles in the structural remodelling and dimerization of the genome during replication and viral RNA packaging¹. The analogy between the structural role of retroviral NC proteins and HCV Core protein prompted us to investigate the nucleic acid chaperoning properties of the latter.

We found that the Core protein is a potent nucleic acid chaperone facilitating the hybridization of complementary DNA/DNA and RNA/RNA sequences in vitro. Similarly to other nucleic acid chaperones, HCV Core protein exhibits a broad range of sequence specificity, and once nucleic acid molecules have been refolded, its binding is no longer required to maintain the new conformation². Strikingly, upon binding to the 3' untranslated region (UTR) of the (+)-strand HCV genomic RNA in vitro, the Core protein causes the formation of dimeric viral RNA. The sequence mediating dimerization has been defined by means of deletion mutants and antisense oligonucleotides, and was mapped to a 16-nt long, highly conserved palindrome situated in the SL2 stem-loop of the 3' UTR. Point mutations in the palindromic region completely abolished RNA dimerization and, at the same time, resulted in the inhibition of HCV subgenomic RNA replication³. Our results point to strong analogies between the functions of HIV-1 NC protein and of the Core protein of HCV in virus structure and replication. In addition, these findings lead us to propose a mechanism for HCV genomic RNA dimerization, which could be involved in viral replication and in the genetic variability of HCV by promoting recombination in a manner similar to HIV-11.

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¹Darlix JL et al. *Adv. Pharmacol.* 48: 345 (2000); ²Cristofari G & Darlix JL *Prog. Nucleic Acid Res. Mol. Biol.* 72: 223 (2002); ³Yi MK & Lemon SM *J. Virol.* 77: 3557 (2003)

PP 2.2.

The Design of HIV-1 Infection Laboratory Model in Cotton Rats

Rytik PG, Kutcherov II, Muller WEG, Poleshchuk NN. Research Institute, Minsk, Belarus

Taking into account the high degree of HIV-1 tropism to human organism, and extremely pronounced polymorphism of AIDS clinical manifestations, one can a priori definitely suggest, that the prognosis of real, adequate HIV-infection model creation will be pessimistic. A way out of this deadlock we see in the restriction of our intentions to create not the whole model, but only part of it. It includes one or some infection signs, predetermined directly by the virus, and manifested regularly.

Findings of clinical, morphological and virologic observation of HIV-infected cotton rats proved us that HIV-1 could really cross species barrier. There are evidences of this: fever reaction, relative weight loss by the animals in 3 and more month after injection, apparent impairments of respiratory organs, death of some animals on the background of cachexia, pneumonia, etc.; distinct signs of inflammatory in same organs, and first of all, in spleen followed by degeneration process. All these evidences give the grounds to suppose that HIV-1 replication in the rats have developed very slowly and, perhaps, some times does not lead to complete virion assembling. The phenomenon of viral integration into cell DNA is a permanent sign and it can be used as the main criterion for the creation of the HIV-infection model. This phenomenon reflects the essence of the viral replication and testifies to an infectious process. All the other signs of the infection (clinical, morphological changes, etc.) displaying not permanently and variously should be taking in account also, but not decisive. It is evident, that the proposed HIV-1 infection laboratory model can be applied only narrowly, namely, to test those preparations (vaccines, chemical compounds), that are planned to use as preventive but not curative means. Thus we may state the following: 1) Cotton rats (weight - 70-80 g.) can be used for HIV-infection modeling; 2) the Tested preparations should be administered before challenge-infection. 3) Challenge-infection is induced by injection (intraperitoneally preferable) of animals with a large dose of HIV highly reproductive strain. The infection of male rats is more favorable. 4) The detection of integration phenomenon in animal tissue (spleen or brain) DNA should be done after the 6th month with PCR.

PP 2.3.**Newly Developed Provirus Quantification Assay using Real-time SYBR Green I PCR and its Validation in a Murine AIDS Model.**

Casabianca A, Orlandi C, Fraternale A and Magnani M. Institute of Biological Chemistry "Giorgio Fornaini", University of Urbino, Urbino (PU), Italy

In this study we present a newly developed real-time SYBR Green I PCR assay for provirus load quantification in a murine model of AIDS, (i.e., LP-BM5 infection). This murine model is used in preclinical studies of antiretroviral therapy for its similarities to human AIDS. The SYBR Green methodology does not require the use of gene-specific hybridization probes, making this method easy, rapid and flexible. Our quantitative analysis combines the use of a simple, low contamination risk adapted procedure for DNA extraction, and an SYBR Green I mixture formulated in our laboratory which eliminates the need for the expensive, commercially available kit. To standardize the BM5d provirus load, an accurate calculation of 18S rRNA reference copy gene was performed and the absolute number of BM5d provirus copies per cell was obtained. The assay shows a linear ($P > 0.99$) wide dynamic range of 8 logs with a limit of sensitivity of one copy BM5d/cell, and a high degree of reproducibility and repeatability with a coefficient of variation for estimated plasmid copy number of 19% and 22% respectively. The applicability of the technique has been successfully tested in a variety of tissues and cells from LP-BM5-infected and AZT+DDI treated mice obtaining an high level of accuracy in proviral load determination. The normalization against the 18S rRNA, having a high degree of interspecies conservation, makes the real-time SYBR Green I PCR assay an excellent candidate for standard provirus quantification protocols.

PP 2.4.

Different Mechanisms of HIV-1 RT-mediated Homologous and Non-homologous Recombination

Kurzynska-Kokorniak A, Jankowska A, Jackowiak P, Alejska M, Figlerowicz M.

Institute of Bioorganic Chemistry Polish Academy of Sciences, Noskowskiego, Poznan, Poland

There are several lines of evidence suggesting that RNA-RNA or RNA-DNA recombination is the main factor responsible for the generation of new retroviral variants, strains or species. Most of the collected data indicate that retroviruses recombine via copy-choice mechanism. It means that recombinants are formed during genome replication when the viral replicase switches from one RNA or DNA template (called donor) to another (called acceptor). Generally, two different types of crossovers can be distinguished: homologous and non-homologous. The former occurs between two identical or almost identical RNA/DNA templates, while the latter involves two different molecules. The studies on replication of the retrovirus genomes also revealed that recombination is inseparable part of the virus life cycle - two homologous recombination events are required to produce dsDNA which is integrated with a host genome. Moreover, the non-homologous recombination is most likely used to capture oncogenes into the retroviral genome.

To better recognize the role of HIV-1 reverse transcriptase (HIV RT) in the studied process, several HIV-1 RT mutants have been generated. To affect recombination frequency, amino acids residues involved in HIV-1 RT - nascent strand interactions were replaced with alanine residues. Mutagenesis was carried out based on the crystal structure of the HIV-1 RT/ RNA:DNA complex (The EMBO Journal Vol. 2, No. 6, pp 1449-1461,2001; pdb code: 1HYS). Then, the polymerase activity of all mutants was tested. Only five mutants displaying similar or little lower activity than wt HIV-1 RT were selected for further experiments. Their ability to mediate homologous and non-homologous crossovers were examined in the recombination in vitro system. This demonstrated a diverse effect of the introduced changes on the frequency of homologous and non-homologous recombination. Some mutations increased, while others decreased recombination capacity of HIV-1 RT. There were also mutants affecting only one type of recombination events. Such a result suggests that HIV-1 RT uses different mechanisms to produce homologous and non-homologous recombinants.

PP 2.5.

Influence of Antigenic Peptide Structure and Delivery System on the Level and Polarization of Immune Response

Maksyutova AV, Bulychiev LE, Maksyutov AZ, Poryvaev VD, Lebedev LR, Ryzhikov AB.
SRC VB "Vector", Koltsovo, Novosibirsk, Russia

The high rate of HIV infection propagation all over the world dictates the strong necessity in effective HIV vaccines. Synthetic antigenic peptides mimicking the antigenic variability of HIV is one of the promising and safe approaches, which induces a broad immune response to HIV variants. The objective of this study was to investigate the influence of the structure of antigenic peptide and antigen delivery systems on the level and polarization of immune response.

We studied the antigenic peptide in the form of peptide library containing 46,000 chimeric peptides and mimicking the antigenic variable loop V3 in gp120 of HIV-1 subtype B. This library showed the positive reaction with serum of HIV-1 infected patients. Peptide library in linear form and in the form of multiple antigenic peptides (MAP) was used for laboratory animal immunization. Rabbits were immunized subcutaneously and mice BALB/c, SPF were immunized intraperitoneally with four delivery systems: Freund's adjuvant, cationic liposomes, microemulsion and virus like particles (VLP). The immune response was controlled by ELISA and ELISPOT.

The results obtained showed the linear peptides inducing the immune response if applicable in Freund adjuvant or VLP. MAP containing 4 or 8 linear peptide chains induced high immune response if administered in solution or in different forms of the delivery systems. The highest level of peptide library specific antibodies was detected in mice immunized with MAP in microemulsion and VLP. MAP4 was more immunogenic comparing MAP8. Immune response in rabbits was similar to those in mice. Polarization of immune response was determined by ratio IgG1/IgG2a of antigen specific serum antibodies and in ELISPOT of mouse spleenocytes. The data obtained indicated the strong prevalence of Th1-type immune response in mice immunized with peptides in microemulsion, whereas of Th2-type was predominant after immunization in Freund adjuvant. So, antigenic peptide structure and the construct of antigen delivery system are essential in the level and polarization of immune response.

PP 2.6.

Identify the Cellular Factors that Interact with Retrovirus Receptors using Yeast-Two Hybrid System

Rezvan M, Tailor CS, Kashan University of Medical Sciences, Iran

Aim: To identify the cellular factors that interact with the cell surface

X-receptor, the receptor Xenotropic and Polytopic Murine Leukemia Virus (X-MLV and P-MLV).

methods: In the yeast forward Two-hybrid system, PGBKT7 XPR was fused with the DNA-binding domain of Gal4 and human fetal liver cDNA library was fused with the transcriptional activation domain of Gal4. We performed a high-stringency scale procedure to screen PGBKT7 XPR against human fetal liver cDNA library and characterized positives by sequence analysis.

Results: We found that the Homo sapiens nardilysin (N-arginine dibasic convertase), mRNA (cDNA clone MGC: 2024 IMAGE: 3138712), and complete cds interact with target protein.

Conclusion: NRDC, as a potential interaction partner for PGBKT7 XPR might be involved in the substrate recognition binding sites, and the acidic domain which might serves as a regulatory domain for polyamines and perhaps for protein-protein interactions, and in various physiological processes. Given these results, our goal was to identify a protein that interacts with the amino terminus of the X-receptor. Further researches on this protein, should be clarify that it may acts as a signaling protein.

PP 2.7.

HIV-1 5'UTR Functions as a Riboswitch Regulating Genomic RNA Replication and Recombination

Urbanowicz A, Jankowska A, Berkhout B, Figlerowicz M.

Institute of Bioorganic Chemistry Polish Academy of Sciences, Noskowskiego, Poznan, Poland

Recombination is one of the major factors generating the very high level of genetic diversity in all RNA-based viruses (RNA viruses and retroviruses). In spite of intensive studies, the mechanism of RNA recombination is still not well understood. The most accepted model assumes that recombinants are formed according to a copy-choice mechanism i.e. due to template switching by viral replicase during nascent strand synthesis. However, in retroviruses, recombination not only stabilizes or destabilizes their genomes but it is also indispensable for viral RNA replication. The reverse transcriptase needs to switch templates at least twice to convert a single stranded genomic RNA into the double-stranded DNA which is integrated with the host genome. The first naturally occurring crossover is supported by short homologous sequences (regions R) located at the very 3'- and 5'-ends of the retroviral genome (within 5'- and 3'UTRs -untranslated regions). Previously, it was shown that HIV-1 5'UTR can adopt two different conformations called BMH (branched multiple hairpin structure) and LDI (long-distance interaction structure). It was also observed that the first recombination event strongly depends on secondary and tertiary structure of HIV-1 5'UTR. Preliminary results suggested that the BMH structure functions as a recombination enhancer. To better recognize the mechanism of recombination events occurring during the HIV-1 genome replication, we tested in vitro how different forms of 5'UTR influence the studied process. Our results confirmed the earlier observations concerning the recombinational activity of BMH and LDI structures. Crossovers occurred more frequently for the mutant adopting the former structure. However, it was noticed that sequence R alone is also able to induce frequent crossovers. Interestingly, we found that a recombinationally active sequence derived from a filogenetically distant virus, brome mosaic virus (BMV), would support HIV-1 RT-mediated homologous recombination at a similar level as the BMH structure and region R. Altogether, these indicate that a relatively short region of homology plays the key role in natural HIV-1 RT mediated recombination. Moreover, our results do not suggest that the BMH structure functions as a recombination enhancer. Rather, they indicate that the LDI structure suppresses homologous recombination. It seems that HIV-1 5'UTR functions as a riboswitch controlling HIV-1 genome replication by inhibiting template switching by RT.

PP 2.8.

A Novel CCR5 Mutation Selectively Affects Immunoreactivity and Fusogenic Property of the HIV Co-receptor in a Slow Progressing HIV Patient

Zhao XY, Lee SS, Wong KH, Chi-Wai Chan K, He ZM, Ma S, Chung-Sing Chan C, Mun-Hon Ng, Zheng BJ. HIV Research Laboratories, Department of Microbiology, the University of Hong Kong; Integrated Treatment Centre, Department of Health; Hong Kong, China

Background: Polymorphism of HIV co-receptors and their ligands, which varies with geographical location, is a determinant of HIV disease progression.

Method: Thirteen HIV patients who had not developed any AIDS-defining condition at least 6 years after initial diagnosis in the absence of treatment were studied for the genotypes of their HIV co-receptors and ligands. A novel CCR5 mutation was identified, the underlying mechanism of which was analyzed through a series of in vitro experiments including genomic cloning for cell transfection, immuno-fluorescence assay (IFA) and fluorescence-activated cell sorter (FACS) for detecting the cell expression and membrane fusion assay for co-receptor function.

Results: A Nepalese heterozygous carrier of a CCR5 mutant, designated 118delF, has remained clinically AIDS-free for at least 6.5 years. The mutation is characterized by 3 base pair (bp) deletion at 352-354 in the CCR5 open reading frame resulting in the deletion of phe-118 residue located in the third transmembrane domain. The mutant protein has retained antigen specificity near the third extra-cellular loop, but the antigenic specificity of N terminal domain is altered, and that of the second extra cellular loop is reduced. Results of fusogenic assay further confirmed that the mutation has abrogated HIV co-receptor activity. Analysis of T lymphocytes from the index patient using the same panel of antibodies suggested that CCR5 118delF is the dominant allele in the heterozygous carrier. The patient did not show other genetic defects in CCR5 and CXCR4, or their respective ligands.

Conclusion: The 118delF mutant of CCR5 brings to a conformation change to the seven transmembrane G protein and transforms its function to support HIV-1 entry. Heterozygous carriage of the mutant gene might account for clinical resistance to HIV disease progression in the patient.

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*Present author: Xiu-Ying Zhao, Department of Microbiology, the University of Hong Kong, University Pathology Building, Queen Mary Hospital, Hong Kong SAR, China. Tel: (852)-2855-4380; Fax: (852)-2855-1241; Email: zhaoxiuying2001@yahoo.com

PP 2.9.**The P40 ORF1 Product of The Human LINE-1 Retrotransposon Possesses Sequence Similarities To HIV-1 Gag**

Zhou JL, Kim SJ, Kirou KA, Crow MK. Hospital for Special Surgery, New York, USA

The human genome contains approximately 516,000 copies of long interspersed nuclear elements (LINEs or L1s), comprising 17% of an average human genome. While most L1s carry a variety of internal mutations and 5' truncations, a haploid human genome has about 90 L1s with intact open reading frames (ORFs). A full length L1 is 6 kb long and contains two untranslated regulatory regions; ORF1, which encodes a 40 kd RNA binding protein (p40); and ORF2, which encodes a reverse transcriptase (RT) and an endonuclease. This genetic structure has some similarities to that of the human immunodeficiency virus type-1 (HIV-1). We hypothesized that L1 p40 represents a homologue of retroviral gag proteins, with implications for its function in formation of ribonucleoprotein particles and retrotransposition.

Among many clones bearing mutations and truncations compared to an L1 consensus sequence, two intact L1 ORF1 sequences were cloned from PCR-amplified cDNA from a human T cell (clone T3) and from human teratocarcinoma cell line NTera2d1 (clone C25), reported to express L1 mRNA. Multiple and distinct regions of similarity were observed between predicted amino acid residues of L1 p40 and the HIV-1 (HXB2) gag. The extent of homology with HIV-1 sequences distinguished some subgroups, with the level of homology greater with groups A, B, C, D, and others, and homology with HIV-1 groups O and M and HIV-2 more limited. These segments of homology included functional regions of HIV gag, such as the myristylation and membrane binding site in Matrix, the p1-p6 cleavage site, and the leucine triplet motif in p6. Overall, the percent homology between L1 p40 and HXB2 gag is: 19% in MA; 10% in CA; 26% in p2; 26% in p7; and 30% in p6. In summary, L1 p40 protein bears sequence homology to HIV gag, with implications for the evolution of these retroviral sequences and the function of the proteins they encode.

PP 2.10.

Automation of Sample Preparation for Quantitative HIV RNA PCR LCx assay

Muller Z, Stelzl E, Kessler HH. Department of Clinical Microbiology, Szekesfehervar, Hungary, Molecular Diagnostic Laboratory, Institute of Hygiene, KF-University, Graz, Austria

Molecular assays for quantitation of the human immunodeficiency virus type 1 (HIV-1) load in plasma have been shown to be important for the monitoring of HIV-1-infected patients and determination of the prognosis. Efforts have been made to achieve full automation of molecular assays for detection of HIV-1. In the present study, the ABBOTT LCx HIV RNA Quantitative assay was evaluated in conjunction with automated HIV-1 RNA extraction on the MagNA Pure LC instrument and compared to the conventional LCx HIV RNA Quantitative assay, which uses a manual nucleic acid extraction protocol. Accuracy, linearity, and interassay and intra-assay variations were determined. The performance of the assay in a routine clinical laboratory was tested with a total of 105 clinical specimens. When the accuracy of the LCx HIV RNA Quantitative assay with the automated sample preparation protocol was tested, all results were found to be within ± 0.5 log unit of the expected results. Determination of linearity resulted in a quasilinear curve over 3.5 log units. For determination of interassay variation, coefficients of variation were found to be between 21 and 66% for the LCx HIV RNA Quantitative assay with the automated sample preparation protocol and between 10 and 69% for the LCx HIV RNA Quantitative assay with manual sample preparation. For determination of intra-assay variation, coefficients of variation were found to be between 7 and 25% for the LCx HIV RNA Quantitative assay with the automated sample preparation protocol and between 7 and 19% for the LCx HIV RNA Quantitative assay with manual sample preparation. When clinical samples were tested by the LCx HIV RNA Quantitative assay with the automated sample preparation protocol and the results were compared with those of the LCx HIV RNA Quantitative assay with manual sample preparation, 95% of all positive results were found to be within ± 0.5 log unit. In conclusion, the assay with automated sample preparation proved to be suitable for use in the routine molecular laboratory and required significantly less hands-on time.

PP 2.11. Intracellular Concentration of Indinavir (IDV) in Patients with AIDS Receiving Two Different Dosages of Indinavir/ritonavir (IDV/rtv)

Garraffo R, Lavrut T, Simonet P and Pugliese P.

Nice University Hospital and Cannes General Hospital, France

Objective: To determine concentrations of IDV in peripheral blood mononuclear cells (PBMCs) of HIV infected patients receiving either 400/100 or 800/100 mg of IDV/rtv bid.

Methods: 17 patients receiving an IDV/rtv plus a dual nucleoside analogue therapy participated in the study, 8 of them received a 400/100 bid dosage regimen while the others (9) received 800/100 mg. PBMCs were isolated by density gradient centrifugation and cell counts estimated. All the blood samples were drawn at steady state since the median duration of treatment was 40 and 36 months for each group respectively and IDV concentrations in plasma and cells were assayed by HPLC.

Results: The median age, weight, viral load and CD4 counts were 39 years, 71 kg, 39 cp/ml and 704/mm³ for the 400/100 mg group and 40.5, 54.5, 39 and 561.5 for the 800/100 mg group. None of them was receiving an associated drug able to induce or inhibit hepatic drug metabolism. The mean ($\pm$ SD) intracellular concentrations observed in the two groups were statistically different at trough level: 4.92 ± 2.13 vs 8.05 ± 1.86 mg/L ($p = 0.04$), but not at the peak level: 29.38 ± 15.89 vs 38.91 ± 27.5 mg/L ($p = 0.1$). The IC/plasma ratio was higher with the 800/100 mg group for trough 7.45 vs 4.87 but not at the peak level 6.26 vs 6.78 .

Conclusion: The RTV booster effect allows to increase the intracellular penetration of IDV providing an intracellular/plasma ratio of at least 4. It appears that both IDV/rtv regimens provide intracellular concentrations widely above the IC₅₀ of the viruses, however the 800/100 dosage regimen appears more secure to maintain high trough levels at the sites of viral replication. The reduction of IDV dosage from 800/100 to 400/100 mg bid would not result in a significant risk of insufficient intracellular trough levels.

PP 2.12.

Effect of HIV Protease Inhibitors on P-glycoprotein Expression in Peripheral Blood Mononuclear Cells: an in vivo and in vitro study.

Le Saint C, Charnay Y, Lafeuillade A, Vincent JP and Cupo A.

Institut de Pharmacologie Cellulaire et Moléculaire UMR-CNRS 6097, Valbonne, France; Hôpitaux Universitaires de Genève, Division de Neuropsychiatrie, Genève, Suisse; Unité Infectiologie, Hôpital Chalucet, rue Chalucet, Toulon, France

P-glycoprotein (P-gp) is an efflux pump for a variety of drugs and is responsible for the development of multidrug resistances and treatment failures. HIV protease inhibitors (PIs) have been shown to be substrates of P-gp. Expression of the protein in plasma membrane of HIV infected lymphocytes leads to increase drug efflux and contributes to decrease the intracellular drug content. The aim of the present study was to correlate the intracellular content of HIV drugs in peripheral blood mononuclear cells (PBMCs) with the expression of P-gp, both in vitro and in HIV infected patients.

We have developed a mouse monoclonal antibody against a fusion protein involving a large part of the human P-gp. Balb/C mice were immunized with the chimeric protein and monoclonal antibodies (mAbs) were produced. The mAbs were selected using a western blot screening. The H7 clone recognized a 170 kDa protein corresponding to P-gp with a good affinity and specificity. The P-gp expression was studied in an in vitro model using human control PBMCs incubated with different PIs (Indinavir, Ritonavir, Saquinavir and Nelfinavir) and in PBMCs of HIV infected patients. Under Saquinavir treatment, the P-gp expression in PBMCs seem to be lower than those observed in Indinavir and Ritonavir treated PBMCs. Our preliminary data in patients seem to indicate that in HIV infected patients the P-gp expression is highly different from one patient to another.

PP 2.13.**The intracellular content of phosphorylated metabolites of AZT and d4T may be quantified in HIV infected patients by two independant specific immunoassays.**

Le Saint C, Menguy V, Lafeuillade A, Vincent JP and Cupo A.

Institut de Pharmacologie Cellulaire et Moléculaire UMR-CNRS 6097, Valbonne; Unité Infectiologie, Hôpital Chalucet, Rue Chalucet, Toulon, France

Introduction Highly active antiretroviral therapy improves rates of mortality and morbidity due to HIV infections. Unfortunately, clinical failures are observed partly due to inefficient cellular concentration of drug enable to suppress the viral load. The determination of intracellular contents of drugs in targets cells should contribute to optimise the antiviral treatment by a therapeutic drug monitoring.

Methods : We have developed highly specific and sensitive radioimmunoassays directed against AZT and d4T. The determination of the AZT and d4T phosphorylated metabolites contents were performed after anionic chromatography (Sep Pak cartridges) followed by a phosphate treatment of samples. The intracellular levels of the three AZT and d4T metabolites were measured both in an in vitro model using control human PBMCs and in PBMCs of HIV-infected patients under AZT or d4T treatment.

Results : The antibody titers of the anti-AZT and antid4T antisera used in this study were 1/70,000 and 1/200,000 respectively. The antibody affinity (IC_{50}) towards AZT and d4T were found to be $2.15 \pm 0.2 \cdot 10^{-9}$ M (mean $\pm$ SD, n=22) and $4.5 \pm 0.3 \cdot 10^{-9}$ M (mean $\pm$ SD, n=15) respectively. The minimal detectable values of the RIA tests, corresponding to the amount of AZT or d4T able to inhibit 20 % of the antigen-antibody binding, were 20 ± 4 fmol (mean $\pm$ SD, n=22) and 50.45 ± 4 fmol (mean $\pm$ SD, n=15). These antibodies neither the other nucleoside inhibitors of reverse transcriptase used in HIV therapy nor their biological phosphorylated metabolites. The intracellular contents of the phosphorylated forms of AZT and d4T respectively were determined in an in vitro model using control human peripheral blood mononuclear cells. Moreover, the AZT and d4T plasma contents and the AZT and d4T phosphorylated metabolites intracellular contents were measured in 28 patients infected by HIV and treated by a polytherapy regimen.

Discussion : In both the in vitro and in vivo models the AZT metabolism appeared to be more efficient than the d4T metabolism. The d4T metabolism determined in HIV infected patients appears to be very different from one patient to another. In contrast, in all the AZT treated patients we tested, we can detect the three phosphorylated metabolites of AZT. The indirect methods we developed offers the opportunity to detect and quantify not only the AZT and the d4T but also all the phosphorylated metabolites of AZT and d4T. Taken together these measurements should constitute an indication of the intracellular metabolism status of HIV-infected patients and should help to better understand therapeutic failures

PP 2.14.

Low Impact of MDR1 Genotype on the Pharmacokinetic (PK) Parameters of Indinavir (IDV) in HIV-Infected Patients Treated or Not with Low-dose Ritonavir (RTV)

Solas C, Poizot-Martin I, Simon N, Bourgarel-Rey V, Dinh T, Sampol-Manos E, Villard PH, Gastaut JA, Lacarelle B.

Timone Hospital, Sainte-Marguerite Hospital, UMR-CNRS 6032, University of Méditerranée, Marseille, France

Introduction: The P-glycoprotein (P-gp), encoded by the MDR1 gene, has been involved in the PK variability of protease inhibitors (PI). Discordant results have been recently found between plasma PI concentrations and the C3435T polymorphism associated with a lower P-gp expression. This study investigated the impact of the C3435T polymorphism on the PK parameters of IDV associated or not with RTV.

Methods: In a prospective study, 28 caucasians patients receiving 2 NRTIs plus either IDV alone (n=14) or associated with RTV 100mg BID (n=14) were enrolled. IDV plasma concentrations were determined by HPLC method. A population PK analysis was performed using a non-linear mixed-effects model. The C3435T polymorphism was determined by analysis of the melting curve after hybridization with fluorescence resonance energy transfer probe on a lightcycler real-time PCR system. Quantification of MDR1 transcript was performed using real-time PCR analysis.

Results: IDV population PK was described using a one-compartment model with first-order absorption. The covariates assessed for their effect on IDV PK parameters were the MDR1 genotype status, the amount of mRNA and the presence or not of RTV. In the final model RTV and the genotype status were identified as significant covariates on the oral clearance (CL) and the absorption rate constant (K_a), respectively. PK parameters estimations (95% CI) were as follow: CL with or without RTV: 26,3 L/h (23-30) and 42,3 L/h (38-46), volume of distribution (V): 69,9 L (65-75) and K_a : 2,95 h⁻¹ (1,05-4,85) for the 3435C/C genotype, 5,91 h⁻¹ (4,03-7,79) for the 3435C/T genotype and 3,22 h⁻¹ (1,15-5,29) for the 3435T/T genotype.

Discussion: MDR1 genotype did not significantly influence the CL and V of IDV but had an effect on the K_a . Patients with the 3435C/T genotype had a higher K_a compared with patients with the 3435C/C or T/T genotype. Differences observed in the K_a between the different MDR1 genotypes could not be linked to differences in P-gp expression. The presence of RTV significantly reduced the IDV CL and its interindividual variability. Therefore, the wide interindividual variability observed in IDV plasma concentrations could be related to hepatic metabolism variation rather than to the genetic status of MDR1.

PP 2.15.

CD4 and CD14 Receptors Down-modulation by Potent Microbicide Lithium-Iodophore

Davtyan TK, Hakobyan IS, Gabrielyan ES.

CJSC "Armenicum" Clinical Centre, Yerevan, Armenia

A low molecular weight α -dextran and polyvinyl alcohol inclusion complex with iodine-lithium have been evaluated as nontoxic either for human and animals antimicrobial agent for systemic intravenous application. This lithium-containing iodophore (LCI -"ArmenicumTM") displayed marked bactericidal and virucidal activity against *E. coli*, *S. aureus*, *S. typhimurium*, *S. pyogenes*, *Y. enterocolitica* and HIV-1, HSV-1, MEV and polio virus during 0.5-30 min exposures in higher dilutions in which iodine concentration varies within a relatively low concentration. LCI exhibits low range cytotoxicity on human whole blood cells, mononuclears and tumor cell lines. LCI modulates antimicrobial host defense mechanisms including microbial cells ingestion by phagocytes and phagocytic cells undergo to the burst of oxygen consumption. LCI dose- and time- dependent manner down-modulate phagocytosis due to LCI interaction with CD14 receptors and regulate the oxidative burst of phagocytic cells depending on the presence of inflammatory response stimulators. LCI induce CD4 receptor down-modulation by rapid CD4 internalization and slower receptor reexpression. LCI blocks CD4-receptor of CD4 T-lymphocytes and inhibits the interaction of HIV gp-120 protein with its specific receptor as well as significantly reduces the HIV-induced CD4 T cell death and syncytia formation in vitro. Thus, LCI could represent a candidate topical microbicide to protect against HIV-1, HSV-1 and bacteria as an innovative approach to prevent sexually transmitted infections by acting both as a chemical and physical barrier against pathogens and as a potent topical anti-inflammatory agent.

PP 2.16.

HIV-1 decoy TAR and vif siRNA Expressed as a Single RNA Molecule under the Human U6 Promoter Enhanced the Inhibition Efficacy of HIV-1 Replication in Transduced Cells.

Barnor JS, Miyano-Kurosaki N, Abumi Y, Shiina H, Ishikawa K, Yamamoto N, Osei-Kwasi M, Ofori-Adjei D, and Takaku H.

Department of Life and Environmental Science and High Technology Research Center, Chiba Institute of Technology, Chiba-Japan; National Institute of infectious Diseases, AIDS Research Center, Tokyo-Japan; Noguchi Memorial Institute for Medical Research, Department of Virology, Accra-Ghana, and Tokyo Medical and Dental University, Tokyo, Japan

Background: The sequence-specific degradation of cognate mRNAs by short interfering 21-23 mer double-stranded RNA (siRNAs) had been a recent molecular tool for disrupting viral mRNAs through a phenomenon known as RNA interference (RNAi). For high and sustainable inhibition of HIV-1 replication in the cells due to siRNA phenomenon, the decoy TAR RNA mechanism was additionally employed for complementation. Thus, HIV-1 decoy TAR RNAs dummy the Tat protein for competitive interaction, and mediate down-regulation of the level of enhanced gene expression from the LTR promoters. Here we show that a novel construct that simultaneously expresses HIV-1 decoy TAR and vif siRNAs as a single transcriptional unit, and separated by the endogenous dicer in the cells, strongly enhanced the inhibition efficacy of HIV-1 replication.

Objectives: Since the role of vif in the infectivity and pathogenicity of HIV-1 is indispensable in the target cells, we sought to establish effective therapeutic target sites within the vif gene that could interfere with the vif-dependent infectivity by siRNAs and decoys in the cells. To achieve sustainable inhibition of HIV-1 in the cells, the vif siRNA was fused to the decoy TAR RNA for complementation.

Design: The siRNA was fused to the decoy TAR RNA by a linker that is recognized by the endogenous dicer for cleavage into their respective components.

Results: In vitro cleavage assay confirmed a high cleavage affinity of the substrate, consequently, the effect of siRNA and the decoy TAR, mediated >80% inhibition of HIV-1 replication.

Conclusion: Targeting the HIV-1 genome with simultaneous intracellular expressed decoy TAR and vif siRNAs could lead to an effective gene therapy strategy for the control of HIV/AIDS.

PP 2.17.**Novel Dimerization Inhibitors acting at the Nanomolar Level : a class of antiproteases to overcome drug resistance in HIV-1 chemotherapy**

Collinet B, Bannwarth L, Boggetto N, Dumond J, Ongeri S, Merabet N, Van Baelinghem L, Sicsic S, Reboud-Ravaux M.

Laboratoire d'Enzymologie Moléculaire et Fonctionnelle, Institut Jacques Monod, UMR 7592, CNRS-Universités Paris 6 & 7, Paris, France ; Laboratoire de Reconnaissance Moléculaire et Synthèse, Biocis, UMR-CNRS C8076, Faculté de Pharmacie, Université de Paris-Sud, Châtenay-Malabry, France

A major limiting factor in the treatment of HIV-1 infection is the emergence of viral strains that show resistance to protease inhibitors. Remarkably, the antiparallel β -sheet region formed by interdigitation of N- (residues 1-4) and C- (residues 96-99) terminal strands of each protease monomer has been found to be highly conserved in most HIV-1 isolates and some HIV-2 isolates. Moreover, this β -sheet contributes close to 75 % of the total Gibbs free energy of dimerization. We demonstrated that HIV-1 protease dimer is disrupted with loss of activity by lipopeptides ($K_i = 5$ nM; Dumond et al., 2003, Biochem. Pharm., 65, 1097-1102), guanidinium-based molecules ($K_{50} = 150$ nM ; Breccia et al., 2003, J. Med. Chem., 46, 5196-5207) and constrained molecular hairpins ($K_{50} = 560$ nM ; Bouras et al., 1999, J. Med. Chem. 42, 957-962). The second generation of molecular hairpins based on quinolin spacers lead to new molecules efficient at 80 nM. Their mechanism of action was identified using Zhang's kinetic analysis and physico-chemical methods (fluorescent probe, gel filtration). Their efficiency against mutated proteases displaying some of the mutations found in resistant variants was analyzed. In conclusion, several of the above molecules acting at the nanomolar level may provide novel therapeutic approaches to AIDS.

PP 2.18.

Sulfonic Acid Polymers as Extracellular HIV-1 Tat and gp120 Proteins Antagonists

Bugatti A, Urbinati C, Goffi F, Camozzi M, Liekens S, De Clercq E, Presta M, Rusnati M.
General Pathology and Immunology, Department of Biomedical Sciences and Biotechnology,
University of Brescia, Italy. & Rega Institute for Medical Research, Leuven, Belgium

Heparan sulfate proteoglycans (HSPGs) can be considered as main modulators of HIV-1 biology. By binding to gp120, HSPGs mediate HIV attachment to the extracellular matrix and to target cells prolonging virus infectivity and influencing viral tropism. Also, HSPGs bind to the extracellular form of HIV-1 Tat that contributes to the onset of AIDS-associated pathologies. This latter interaction mediates Tat accumulation in the extracellular matrix, Tat uptake and transactivation in target cells. These observations point to HSPGs as possible targets for the development of anti-HIV therapies. On these bases, we investigated the anti-gp120 and anti-Tat potential of a series of synthetic sulfonic acid polymers (SSAPs): poly(4-styrenesulfonic acid) (PSS), poly(anetholesulfonic acid) (PAS), poly(vinylsulfonic acid) (PVS) and poly(2-acrylamido-2-methyl-propanesulfonic acid) (PAMPS). By using the BIAcore technology we demonstrated that all the SSAPs tested are able to prevent the binding of both gp120 and Tat to surface-immobilized heparin, an experimental condition that resembles the binding of the two viral proteins to cellular HSPGs. The inhibitory potency of the SSAPs decreases with increasing concentrations of the viral proteins, indicating a competitive mechanism of action. We also evaluated the capacity of the SSAPs to inhibit Tat-HSPGs interaction in cultured cells and the subsequent biological effects. All the SSAPs tested were able to inhibit: i) the binding of Tat to HSPGs expressed on the surface of chinese hamster ovary (CHO) cells; ii) the internalization of Tat fused to the green fluorescein protein in HL3T1 cells; iii) the transactivating activity exerted by Tat in HL3T1 cells. On the other hand, it has been demonstrated that SSAPs block gp120/CD4 interaction and possess anti-HIV activity (Mohan, P. et al. 1992 Antiviral Res. 18:139-150). In conclusion, the SSAPs can prevent the interaction of both gp120 and Tat with HSPGs and some of the biological effects related to these interactions. These data call for additional experiments aimed to evaluate SSAPs as multi-target prototypic molecules able to prevent/retard HIV-infection and AIDS-associated pathologies.

PP 2.19.**Mutations Conferring Drug-resistance of the Reverse Transcriptase of Human Immunodeficiency Virus Subtype G.**

Garaev MM, Pazilin AS, Shemshura AB, Saukhat SR.

Institute of Virology, Moscow, Russia

HIV in Russia is genetically diverse with 95% prevalence of subtypes A, B, C and G. The majority of subtype G isolates are epidemiologically linked to the previously reported nosocomial common-source HIV-1 infection of children and their mothers in Rostov-on-Don, Southern Russia. Our objective was to study the mutations in the reverse transcriptase (RT) of HIV-1 subtype G that confer resistance to RT inhibitors. Patient cohort consisted of 15 individuals infected from a common source in 1989 in Rostov-on-Don and in the Kalmyk Republic. All received combined antiretroviral chemotherapy that included both nucleoside (NRTI) and non-nucleoside (NNRTI) RT inhibitors, and protease inhibitors. RNA was isolated from the peripheral blood lymphocytes collected in 2000-2001, and RT gene was reverse-transcribed, amplified, and sequenced. Phylogenetic analysis of the bp 87-817 region of the RT genes in the context of the Gene Bank data revealed three clusters: one joining sequences of the G subtype; the other, of the J subtype; and in third, of other subtypes. Mutation patterns conferring AZT- resistance of HIV subtype G were not significantly different ($p>0.1$) from the patterns described for subtypes A, B, C, D, and F. Mutations conferring resistance to NRTI (ddI, d4T, 3TC) and NNRTI (nevirapin) were also concordant with mutations published in the HIV sequence compendium for other HIV subtypes. One isolate from a patient who interrupted AZT-therapy for the last 3 years had a L921 mutation described previously as conferring resistance to foscarnet, while lessening the effects of AZT-resistance mutations. In other patients, a two-year interruption of AZT-therapy resulted in a full reversion to the wild-type HIV-1 G RT sequence. Thus, we had for the first time characterized the evolution of drug- resistance mutations in the reverse transcriptase of HIV-1 subtype G circulating in the Russian Federation.

PP 2.20.

Effects of Antiretroviral Exposure and Genotypic Mutations in Predicting Phenotypic Resistance to Atazanavir (ATV), Lopinavir (LPV), and Tenofovir (TDF) in Patients Naïve to these Drugs.

Samson P, Rutstein R, Schnittman S, Ortiz A, Graham B, Fenton T, Aldrovandi G, and the Pediatric AIDS Clinical Trials Group P1020A Study Team. Boston, USA

BACKGROUND: The following factors were evaluated as potential predictors of phenotypic resistance to ATV, LPV, and TDF among 56 heavily experienced patients naïve to these drugs: 1) mutations at specific codons, 2) the number of geno PRO mutations (#PRO) and RT mutations (#RT) and 3) previous exposure (EXP) to other specific ARVs. **METHODS:** Study sample. Patients undergoing screening for PACTG1020A. Pheno-resistance scores (PRS) were calculated as the log₁₀ IC₅₀ Fold Change (Virologics®). Geno-mutations at the PRO & RT codons were assessed. Previous EXP to ARVs (3TC, ABC,D4T, DDI, DDC, ZDV, DLV, EFV, NVP, APV, LPV, NFV, IDV, RTV,SQV, ADE, HU) was categorized into: no EXP,current EXP or past EXP. Our previous research had created models which identified specific codons at which mutations made; unique & significant contributions in predicting PRS of ATV, LPV & TDF. The extent to which information concerning exposure to other ARVs, along with the total #PRO and #RT mutations, enhanced this prediction was assessed as follows: 1) Univariate F-tests identified drugs to which EXP significantly predicted PRS to ATV, LPV & TDF; 2) Univariate Correlations tested if the #PRO or #RT mutations predicted the PRS of ATV, LPV, TDF; 3)Variables with significant effects on these tests, along with the codons previously identified, were entered in Backwards Stepwise Regressions predicting PRSs of ATV,LPV & TDF. **RESULTS** ARV exposure was not significantly associated with PRS of ATV, LPV & TDF. The one exception was that the geometric mean LPV IC₅₀ Fold Change increased with APV use: No EXP (4), Past EXP (15), Current EXP (34) (p .003). Correlations between PRS of ATV, LPV & TDF, and: 1) #PRO mutations were .88*,.72*,.39* and 2) #RT mutations were .49*,.46*,.28 (*P<0.01).Multiple regression models identified the variables which made unique & significant contributions in predicting ATV, LPV, & TDF PRS. [An/: mutations at PI: 13,54,73,84, RT: 215, along with #PRO; R²-.91], [LPV: mutations at PI: 10,33,54,67; R²-.86]; [TDF: mutations at RT210;R²=0.20]. ARV EXP did not show significant effects in these models.

CONCLUSIONS: Information concerning geno-resistance was much more predictive of pheno-cross resistance to ATV, LPV, & TDF than was current or past exposure to specific ARVs. Geno-data accounted for high percentages of the variability in PRSs of ATV & LPV, but prediction of TDF PRS was not as accurate.

PP 2.21.**Microbicidal and Virucidal Action of Antioxidants and their Interaction with Iodophores**

Hovhannisya HGn. CJSC "Armenicum" Clinical Centre, Yerevan, Armenia

Microbicidal and virucidal action of some natural antioxidants and their chemical derivatives has been studied on the model of E.coli K-12 cells, temperate and virulent DNA, RNA and ssDNA containing bacteriophages. High microbicidal and virucidal effect has been revealed in the result of treatment by L-cystine, L-cysteine, N-acetyl-L-cysteine and ascorbic acid. These antioxidants suppress infection, intracellular morphogenesis, maturation and inactivated all kinds of virions. Other antioxidants (e.g. L-methionine, S-methyl-L-cysteine, L-tryptophane, L-isoleucine, uracil, thiamine) don't influence on cells or viruses viability.

All tested antioxidants completely inactivate antibacterial and antiviral activity of oxidative iodophores such as dextrin-iodine, polyvinylalcohol-iodine and their mixture known as "Armenicum" drug used for HIV-treatment by intravenous administration, but keep their initial activity. As human organism is rich with various antioxidants, iodophore drugs insignificantly lose their activity during parenteral administration. The antioxidants and their derivatives can be promising for treatment of bacterial and viral emerging infection diseases, including HIV-infection.

PP 2.22.

Full Transcriptome Analysis of Genes Altered by HIV in Macrophages.

Ottones F, Lejeune M, Manchon L, Piquemal D, Commes T, Marti J.

Institut de Génétique Humaine, CNRS UPR 1142, Skuld-Tech, Université Montpellier II, Montpellier, France

Macrophages are amongst the initial cell types infected by HIV-1 despite mechanisms of innate immunity conferred through the interferon response. In contrast to infected T-cells, macrophages show no extensive virus induced cytolytic effect, which may be due to the induction of anti-apoptotic genes like those of the B-cell CLL/lymphoma (BCL) family. Macrophage effector functions of phagocytosis, intracellular killing, antigen-presentation, chemotaxis and cytokine production are disrupted following HIV-1 infection facilitating the development of opportunistic infections and thus contributing to the pathogenesis of AIDS. Although monocytes are infected with HIV, only differentiated macrophages are able to sustain active viral replication. They represent both a reservoir and a source for dissemination of the virus to other tissues throughout all stages of infection. In order to further our comprehension of the role of macrophages in HIV infection, this study sought to identify HIV-induced changes in macrophages by monitoring gene at the expression level. The Serial Analysis of Gene Expression (SAGE) technology is ideal to investigate full expression profiles, including new genes (Velculescu VE et al, 1995). We constructed 4 SAGE libraries of HIV-1-infected monocyte-derived macrophages (MDM) or Mock-infected MDM at 4 and 24 hours after infection. We have already sequenced 97.787 SAGE tags from these libraries. After tags identification, using the BioTag and ProbaTag softwares developed in our laboratory, the comparison of these libraries revealed 24.587 different tags. We observed 537 genes significantly modulated ($p < 0.01$) by HIV infection at 4 hrs post-infection and 138 at 24 hrs post-infection, with respectively 27% and 23% of unknown genes. Identified genes have been classified in different functional groups, whose proportions are affected differently by HIV-1 infection. We are now focusing our study on specific targets which may explain how HIV-1 escapes the interferon response and apoptosis. This global study presents the first full transcriptome analyses of HIV-1-infected macrophages and will undoubtedly give new informations about molecular actors and/or regulatory mechanisms acting in HIV infection and may identify new targets for therapeutic strategies aimed to stimulate macrophage response against HIV.

PP 2.23.**Enhanced Degradation of Drug-resistant HIV-1 Reverse Transcriptase is Mediated through Proteasomal Pathway**

Starodubova ES, Pazlin AS, Karpov VL, Isaguliants MG.

Institute of Molecular Biology, Institute of Virology, Moscow, Russia; Institute of Infectious Diseases, Stockholm, Sweden

Exposure to drugs gives rise to a variety of mutations that alter reverse transcriptase (RT) biochemistry and confer high levels of HIV resistance. We have recently shown that mutations conferring drug-resistance (DR) affect the speed of protein degradation (Isaguliants et al, AIDS Res & Hum Retrovir 2004, 20:191). Half-life of AZT-resistant D67N/K70R/T215F/K219Q-RT was only 5 h as compared to 19 h for the wild-type (wt) RT. Regulated protein degradation within cells is mediated primarily by the 26S proteasome.

Here, we investigated the role of the proteasome-mediated proteolytic pathway in the RT degradation. Genes for RT, D67N/K70R/T215F/K219Q-RT, and A62V/D67N/S68N/K70G/V751/F77L/I115F/F116Y/Q151M/M1 84V/T215Y/K21SQ-RT were transiently transfected into HEK293 cells. After RTs were accumulated (48 h), protein synthesis was inhibited by cycloheximide. Cells were then chased for 6 hours with or without proteasome inhibitors MG132, Epoxomicin and ZL3VS. The retained RT was assessed by Western blotting using polyclonal anti-RT antibodies. The internal controls were α -tubulin, and co-transfected ornithine decarboxylase with a half-life of about 20 min. We found proteasome inhibitors to considerably stabilize both of the DR-RTs. This indicates that the RT degradation in the cell is mediated through the proteasome pathway. Proteasome generates peptides for MHC class I presentation. Our next step would be to find if the increased degradation of drug-resistant RTs has an effect on their presentation and immunogenicity.

PP 2.24.

Parameter Identification of an HIV/AIDS Dynamical Model

Ouattara DA, Bugnon F, Moog C, Raffi F. IRCCyN (Institut de Recherche en Communication et Cybernétique de Nantes), UMR CNRS 6597, & CHU de Nantes, Centre d'Information et de Soins de l'Immunodéficience humaine, Nantes, France

This paper highlights the role of mathematical modeling to give an additional insight for understanding the dynamical evolution of HIV infection. Standard clinical data of 12 infected patients are used to derive biological parameters involved in some elementary mathematical model.

The main goals in this study are listed and include:

- display the variability of parameters from one patient to the other,
- display the variability of parameters from one treatment to the other, for a given patient,
- evaluation of the treatment,
- simple measurements of biological tests can be used to derive much more sophisticated parameters and this is a cost less operation (up to the cost of computation).

Engineering methods are used such as estimation using least square (LSQ) method or adaptive observer.

Introduction

A descriptive overview of the identification of the 3D HIV/AIDS model parameters [1] is given. The model which is used here is the basic 3D model. It includes the dynamics of infected CD4+ T-cells, uninfected CD4+ T-cells and virions.

$$\dot{T} = s - \delta T - \beta T v$$

$$\dot{T}^* = \beta T v - \mu T^* \quad (1)$$

$$\dot{v} = k T^* - c v$$

In this model, T represents the uninfected CD4+ T-cells, T^* represents the infected CD4+ T-cells and v , the free virions. The six parameters s, δ, β, μ, c characterize these dynamics as follows.

Free virus particles infect uninfected cells at a rate proportional to the product of their abundances ($\beta T v$) and are removed from the system at the rate $c v$. $1/c$ represents the natural life span of virions. We suppose in this model that CD4+ T-cells are produced at a constant rate s . It is the simplest way to model production of CD4+ T-cells. μT^* represents the rate at which infected cells are removed from the system. We define by $N = k/\mu$ (the burst size) the total amount of virus particles produced from a one infected cell.

For more details on this model, refer to [1][5].

This model describes the basic dynamics of HIV/AIDS infection and only the primary phases of the infection are described. Many aspects of the infection such as latently infected cells (modeled in a 4D model), response of immune system which can be modeled by CTL, the cytotoxic T-cells (in a 5D model) [2], proliferation of healthy T-cells [3][4], are not included.

Using all these models implies a good knowledge of their parameters - s, δ, β, μ, c for (1) - They are known to change from one patient to other, one HIV type to other and during the HIV/AIDS infection. So, the challenge is to install new estimation methods which can be applied to any patients and in any cases. These methods are mathematical methods and they use clinical data such as viral load and CD4+ T-cells to estimate parameters.

It is important to notice that these methods are non-expensive methods and they enable us to extract essential characteristics of the infection process (e.g. the effectiveness of the infection process which is represented by β ; the life span of virus particles ($1/c$), of infected CD4+ T-cells ($1/\mu$) or uninfected CD4+ T-cells ($1/\delta$); the amount of virions produced by a one infected cell everyday (k), the effect of the therapy on such or such parameter, etc...). All these information are not inevitably perceptible after medical diagnostic of patients.

The identification method, which is used to estimate the parameters in model (1) for different patients, is the least squares method [11][12] - LSQ. It consists in minimizing the least square distance between our model and data. This method is influenced by measurement noise. To circumvent this problem, numerical filters are implemented through the MATLAB® Simulink® environment.

This method is an “off-line” estimation method (estimation is made after data are collected) in opposition to “on-line” estimation methods such as adaptive observers [7][8][9][10] which enable to get a real-time estimate.

The latter is able to give estimates of the parameters progressively with acquisition of data.

The principle objective of this work is to set up methods witch will improve clinical diagnostics of infected HIV/AIDS patients.

With 3D Model, if parameters are known, we can simulate dynamics of T , v and T^* even if the account of infected CD4+ T-cells is not clinically measured. So, in addition to the viral load and the account of healthy CD4+ T-cells, we can have precious information on infected CD4+ Tcells dynamics. Notice that for 4D or 5D models, dynamics of CTL, or latently T-cells must be known by this method.

Since each parameter characterizes one aspect of the disease, we will be able to set up new strategies of treatment witch will target parameters on witch we have to act. Treatments will be simpler and more efficient for patients. These strategies of treatment, with minimal doses of drugs. then with low cost . will simplify patient's life. This is important because currents HIV/AIDS drugs are known to have several drawbacks (diarrhoea, weaken, nausea, neurological disorders) witch can be irreversible.

Results: parameter estimates for different patients

This table presents some data on 3 patients which are considered next.

Birth date	Date of	N°
-dd/mm/yyyy-	seropositivity	
17/09/1953	15/06/1984	788
17/08/1961	17/07/1986	97
29/07/1962	18/10/1990	556

Parameters that are given represent the average values on the estimation period.

1. Patient 97 (43 years old):

Treatment	s	$1/\delta$	β	$1/\mu$	k	$1/c$	s/δ
Invir.+Retr.+Vid.→ Epiv.+Invir.+Retr.	0.56	62.5	5.05E-07	N	522.2	N	35
Epiv.+Norv.+Zer.	0.94	440.3	1.19E-06	46.11	1.54	34.61	414.5

Table 2



Fig. 2

Figure 2 displays the concentration of CD4, T ($CD4/mm^3$) and the viral load, v (ARN copies/ml), versus time t (days).

Here, the day $t_0 = 0$ correspond to 08/20/1996. In a first period of time, this patient is treated by a *Invirase+Retrovir+Videx* therapy (from 17/07/1996 to 24/09/1996). It is followed by a *Epivir+Invirase+Retrovir* therapy (until 06/23/1997). During these two therapies, the production rate of CD4 is estimated at $0.56\text{ }CD4/mm^3$. The life span of Lymphocytes T-CD4 is evaluated at 62.5 days, thus $\frac{s}{\delta} \approx 35\text{ }CD4/mm^3$. These therapies were considered as an immunologic failure for this patient. Remark: note that the rate s/δ is the theoretic equilibrium for the CD4 population in the case of a zero viral load.

The third therapy – *Epivir+Norvir+Zerit* (witch began as from 06/23/1997) – allows increasing the level of CD4 above the value of $400\text{ }CD4/mm^3$.

The rate s/δ is now evaluated as $470\text{ }CD4/mm^3$. Note that the parameter s is dramatically smaller than $1\text{ }CD4/mm^3/j$, however the life span s/δ of healthy CD4 is 8 times larger and yields an acceptable' rate s/δ .

Efficiency of the therapy

Note that the production rate k of virions goes from 522.2 to 1.54 ARN copies/day and the estimate of β is negative after the treatment. The analysis of the change of parameters allows understanding why a given therapy is successful or unsuccessful. In the case of patient 97, the success of the second therapy is due to its action on both k et β .

Thus, infection of healthy CD4+ T-cells by free virus particles and the production of new infectious virions are both stopped by the treatment.

These characteristics are respectively due to **Protease Inhibitors (PI)** and **Reverse Transcriptase Inhibitors (RTI)**.

In fact, RTI aims to block the transcription of the viral RNA by the reverse transcriptase enzyme into DNA. By this action, production of new virions will be stopped (parameter k decreases to zero).

With PI treatment, drug will inhibit maturation of new virions. Then, produced virions will be non-infectious and then, they will be unable to infect new T-cells (parameter β decreases to zero). That suggests that the effect of treatments can't be only modeled on parameter β . Their effects on parameter k must be considered.

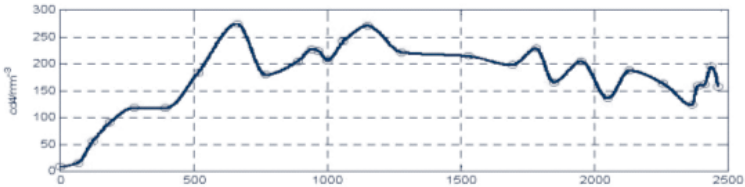
Negative values of parameters will be interpreted later.

Life span of virions

The life span of virions under the second therapy, $1/c$, was evaluated at 35.71 days. This estimate is rather large when compared with other references: $1/c$ ranges from ~ 2.6 days to ~ 4.33 days in [13] and is evaluated at approximately ~ 3 days in [14] for instance. This difference may be explained by the type of virus as well as other phenomena which are not modeled.

Treatment	s	1/ δ	β	1/ μ	k	1/c	s/ β
All the Period	1.21	166.66	5.36E-07	100	-3.06E-01	45.45	201.6
Crix.+Epiv.+Retr	1.32	90.9	6.22E-07	N	6.91	N	119.99
Comb.+Sust.	2.57	83.33	2.05E-06	N	4.84	N	214.16

Table 4



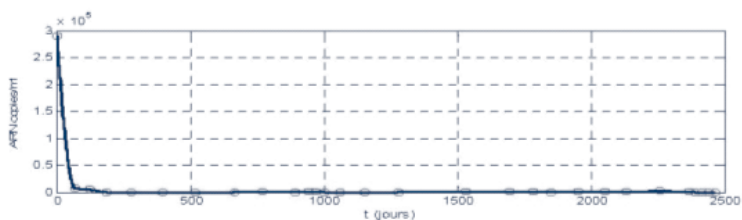


Fig.4

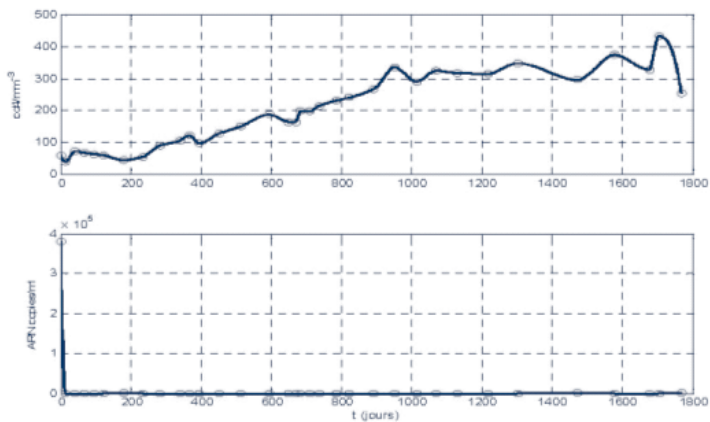
Time t_0 correspond to 11/05/1996. The estimation of parameters shows that from a virological point of view, the production rate k of new virions has significantly decreased thanks to the tri-therapies *Crixian+Epivir+Retrovir* (from 11/05/1996 to 18/12/1998) and *Combivir+Sustiva* (from 11/22/1999 to 01/16/2003), although the parameter β increases and is 3.3 times larger.

This is an immunological failure of the therapy since the CD4+ population does not increase although the viral load is almost zero. It is in accordance with the clinical conclusions since the CD4 load of the patient does not reach the level of 400 CD4/mm³. The estimate of s shows that its immune system was deeply damaged by the infection.

3. Patient 788 (51 years old):

Treatment	s	$1/\delta$	β	$1/\mu$	k	$1/c$	s/β
All the treatment period	0.37	2000	8.21E-08	58.82	67.66	15.38	740
Vid.+Virac.+Zer.	1.04	87	4.83E-06	X	-1.5	27.96	90.48
Sust.+Vid.+Zer.	1.94	166.67	1.05E-05	X	0.017	66.67	223.34

Table 5



With this patient, the infection was stopped thanks to the treatment and the CD4 load increases continuously and stabilizes at around 350 CD4/mm³.

When the therapy *Videx+Viracept+Zerit*, is applied $s=1.04$ CD4/mm³ day The ratio s/δ equals approximately 90.48 CD4/mm³. During this phase of the treatment, the viral load is almost zero and the CD4 load remains weak although it is increasing. Thanks to the therapy, the viral load decreases from 380000 ARN copies/ml (5.58 log) to 0 ARN copies/ml. During a second phase of the treatment the viral load is maintained at a zero level and finally the CD4 load reaches the level of 400 CD4/mm³. As it is the case for patient 97, the increasing of the CD4+ load reflects the equilibrium between the production, s , of CD4 cells and their life span, s/δ , so that s/δ equals 332,34 CD4/mm³. This was made feasible thanks to the treatment.

Approximation and simulation

For this patient, we can simulate the dynamics of the HIV/AIDS disease since we have a sample of the estimate of the 6 parameters.

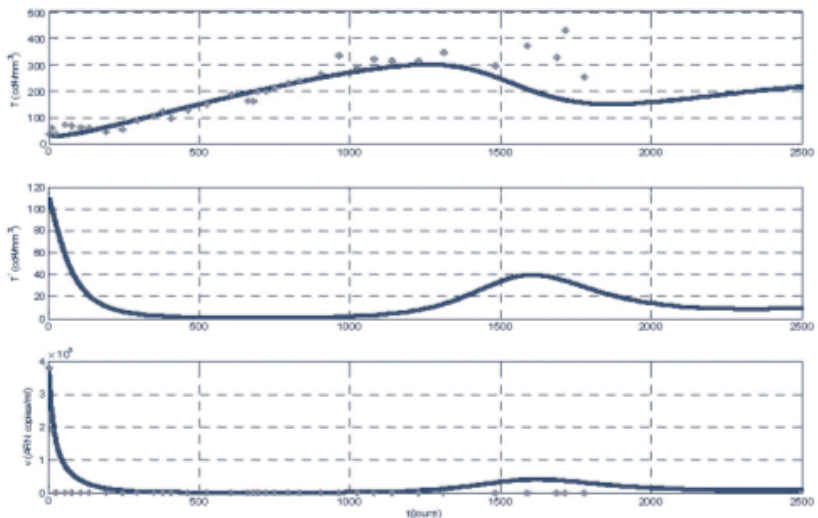


Fig. 5: Simulation with $T^*(0) = 109.88$ CD4/mm³ CD4/mm³.

Figure 5 display the simulation of the dynamics of T^* , T and v with: $s = 0.37$, $\delta = 0.0005$, $\beta = 8.31e-8$, $\mu = 0.017$, $c = 0.065$ and with initial conditions $[T_0 \ V_0] = [59 \ 3.8e + 5]$. T_0 and V_0 represent $T(t)$ and $v(t)$ at time $t=0$

To do simulation, initial condition of T^* must be computed since biological tests do not allow us to measure directly the initial population of infected CD4 cells.

So, we consider the third equation $\dot{v} = kT^* - cv$

$$\Rightarrow T_0^* = \frac{\dot{v}_0 + cv_0}{k} \text{ with } T_0^* = T^*(t=0) \text{ and } v_0 = v(t=0).$$

The simplest way to compute v_0 is to estimate the slope of $v(t)$ at time $t=0$. In this case initial population of infected CD4 T-cells is estimated at 109.88 CD4/mm³.

Through the simulation it is possible to predict the evolution of the disease. In the situation of this study, we are based on the 3D model.

Only 6 parameters are involved s , δ , β , μ , and c . Phenomena such as viral resistance, the existence of latent cytotoxic T-cells are not taken into account. It is possible to pick a more sophisticated model and eventually improve the accuracy of the predictive simulation. The prediction of the efficiency of the therapy is obvious and should allow to anticipate and to choose the “right” and most acceptable therapy.

Conclusions and Perspectives

In this work, preliminary results have been obtained which show that engineering methods provide an alternative and cheap method for analyzing the dynamics of the infection process. It provides an additional insight which may be used

- to evaluate properly the efficiency of a given treatment,
- to predict the evolution of the infection, to adapt the treatment.

For the future, the challenge is to elaborate mathematical algorithms – using mathematical and medical tools – to compute optimal therapies and this, for each patient. Optimal therapy “means the lowest doses of drugs with the best efficiencies: i.e. to maintain viral load under the 50 ARN Copies/ml level and the account of CD4+ upper the 400 CD4/mm³ level”.

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PP 2.25.**The Carboxyl-Terminus of HIV-1 Integrase Facilitates Viral Nuclear Import**

Cunningham C, Topper M, Muesing MA.

Rockefeller University, Aaron Diamond AIDS Research Center. New York, USA

After fusion and entry, the Human Immunodeficiency Virus (HIV-1) must navigate its genome through the cytosol and into the nucleus of its target cells, where integration into the host's chromosomal DNA subsequently occurs. The precise mechanism of nuclear entry, as well as the identity of the cellular factors and the contributions of viral determinants that are essential for it, has long remained elusive. Here, we identify a potent, transferable and unusual nuclear localization signal (NLS) in the carboxyl-terminal domain of HIV-1 integrase (IN). Double and triple mutants of two distinct clusters of basic amino acids within the NLS region of IN were discovered that prevent nuclear import of large, otherwise cytoplasmic IN fusion proteins. Although biochemical and genetic characterization of virions incorporating NLS mutations does not readily identify an overt defect, a quantitative analysis of viral DNA intermediates (early RT, late RT, and 2-LTR circle products) formed during infection of primary lymphocytes and macrophages reveals a striking and specific two-log defect in nuclear import of mutant viral DNA. In addition, these mutations within IN have minimal effects on reverse transcription and do not interfere with obligate catalyses, such as 3' processing and strand transfer, that the enzyme performs during infection. Thus, apart from its obvious role in retroviral integration, HIV-1 integrase specifies a powerful karyophilic signal that is required for productive infection of both dividing and non-dividing cells.

PP 2.26.**Molecular Homology Between Alpha-defensin And Scrub Typhus Rickettsia Orientia Tsutsugamushi 56kd Type Specific Antigen**

Tran MKG, Kirkiacharian S, Maurisson G, Caprani A.

University, Paris Sud XI, Faculty Pharmacy, Chatenay Malabry, Centre Medical Europe, University Paris Jussieu, Paris, France

Introduction: 1) Zhang L.(2002) discovered an alpha-defensin isotype [differing by isoleucine 28 (Ileu 28 or I 28), instead of phenylalanine (Phe or F) in classical commercial alpha-defensin] as the natural protective factor against HIV-1 in long-term nonprogressors remaining alive without treatment. 2) Watt G (2000, 2001) remarked a beneficial effect of sera from scrub typhus Rickettsia (Orientia Tsutsugamushi) [Rick.Or.Tsu.]-infected HIV-1+ patients on HIV-1 replication, suggesting a protective cross-reactive antibody. 3) Tran M.K.G. described a molecular homology between Nef and alpha-defensin (Warsaw Conf., Poland, 2003), then between Nef and Rick.Or.Tsu. 56 Kd type specific antigen (tsa 56) (this Toulon Conf., 2004) centered on the common tetrapeptide GIRY. Objective: To find the precise sequence of the rickettsial cross-reactive protective epitope(s). Methods: We compared the amino acid sequence and tridimensional (3D) structure of alpha-defensin (I 28) and Rick.Or.Tsu tsa 56.

Results:

Commercial alpha-defensin	F
Zhang's alpha-defensin (I 28)	28 IAWLRGQY 21 (reverse lecture 28-21)
Rick.Or.Tsu tsa 56	168 IAWLK -NYA 175
HIV-1 nef (clade AE thailand)	I- WKF- DSA

Aligned R24 and K172 are both basic residues. It is noteworthy that Zhang's alpha-defensin variant (I 28) is 20 times more protective against HIV-1 than commercial alpha-defensin (F 28), pointing to an important role for this isoleucine 28 residue.

Discussion: Rick.Or.Tsu tsa 56 is a perfect molecular mimicry of Zhang's alpha-defensin centered on the tetrapeptide IAWL, with a significant homology spanning 8 residues, suggesting that protection may be mediated by a cross-reactive antibody against HIV Nef sequence IWKFDSEA. The trilogy (Nef, Zhang's alpha-defensin and Rick.Or.Tsu tsa 56) defines 2 homologous linear epitopes (centered respectively on IAWL and GIRY) located in proximity in a 3D space. For clade B and Thailand clade AE, vaccines with these Nef epitopes, or an anatoxine with Rick.Or.Tsu tsa 56, and passive immunotherapy (sera, monoclonal antibodies, Fab, Fv,...) could be designed as an interesting anti-HIV-1 therapy, as this Nef region is relatively conserved inside each clade.

PP 2.27.

HIV-1 Protease Is A Metalloproteinase Containing A Copper-Binding Motif Gly His Lys (GHK) At Residues 68-70

Tran MKG, Kirkiacharian S, Maurisson G, Caprani A.

University, Paris Sud XI, Faculty Pharmacy, Chatenay Malabry, Centre Medical Europe, University Paris Jussieu, Paris, France

Introduction: Antiproteases are very efficient molecules, however they rapidly induce cross-reactive chemoresistance with occurrence of multiple mutations (L10FIRV, K20MR, L24I, D30N, V32I, L33F, M36I, M46IL, I47V, G48V, I50V, I54VML, L63APQ, A71TV, G73SA, V77I, V82AFTS, I84V, N88DS, L90M), rendering their long term efficacy problematic. **Methods:** We undertook a systematic screening of the complete amino acid sequence of HIV-1 protease, looking for some specific motifs which could have escaped to previous investigators. **Results:** There is a classical typical copper-binding motif Glycine Histidine Lysine (Gly His Lys, or GHK) [K stems for Lysine] (Pickart L, 1980) at HIV-1 protease residues 68-70. For example, GHK is found in collagen I sequence, and released after proteolysis as a copper tripeptide (Maquart F.X., 1988). This 68-GHK-70, located far from the catalytic site, classified HIV-1 protease as a member of metalloproteinase family, with 2 symmetrical coppers. The function of copper seems important: Only rarely His 69 is mutated to Tyrosine (Tyr or Y) (treatment by lopinavir) and even then, the replacement of His by Tyr could be non functional, because both residues bind copper, although the copper affinity for His is higher. As HIV-1 Gag contains also GHK, and is the target of HIV-1 protease, it may be that copper, as a metal bridge, could contribute to gag proteolysis.

Discussion: A chemical design of new anti-proteases generation must take in account the chelation by the motif 68-GHK-70 of the 2 symmetrical coppers in protease dimer, to enhance efficacy and perhaps avoid chemoresistance, as far as copper is necessary for HIV-1 functional enzymatic activity. As a metalloproteinase, HIV-1 protease may be attacked by adequate antiprotease simultaneously at this copper Achilles' heel, what has never been done until now.

PP 2.28.

Incorporation of nucleoside analogs into mitochondrial DNA decreases in the presence of p53 protein

Bakhanashvili Mary, Novitsky Elena, Levy Itzhak and Rahav Galia

Unit of Infectious Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel.

Nucleoside analogs (NAs), are potent inhibitors of HIV reverse transcriptase. It is well established that long-term therapy can cause mitochondrial toxicity. Acquired mitochondrial toxicity in patients taking antiviral nucleoside analogs occurs as a consequence of incorporation into mitochondrial DNA by DNA polymerase γ , the polymerase responsible for mitochondrial DNA replication. Although mitochondrial DNA polymerase γ has 3'→5' exonuclease activity, the failure of this proofreading activity to efficiently remove chain terminators may play a role in mitochondrial toxicity of nucleoside analogs. It was recently reported that a fraction of induced tumor suppressor protein p53 translocates to the mitochondria of apoptosing tumor cells. The present study is based on our previous observation that the wild-type p53 with its associated 3'→5' exonuclease activity is able to preferentially remove mismatched nucleotides from DNA and serve as an external proofreader for DNA polymerases. We further investigated the ability of p53 to remove mismatched nucleotides and nucleoside analogs from mitochondrial DNA. Using an in vitro DNA primer extension assay with mitochondrial fraction of H1299 cells (p53-null), it was shown that mismatched nucleotides and various ddNTPs were incorporated into the elongating DNA strand by mitochondrial DNA polymerase γ . Once incorporated, mispaired nucleotide and NA became a poor substrate for 3'→5' exonuclease activity of this DNA polymerase. However, the efficient excision of the incorporated mismatched nucleotides or nucleoside analogs from chain terminated 3' end of the DNA primer was observed in the presence of either purified wtp53 or cytoplasmic fraction of LCC2 cells (expressing high levels of p53). Inefficient excision was detected with cytoplasmic extracts obtained from either MCF-7 cells (expressing low levels of wtp53) or MDA cells (expressing mutant p53). Furthermore, immunoprecipitation of p53 from cytoplasmic extracts of LCC2 cells markedly reduced the exonuclease activity. Thus, the data demonstrate that wt p53 in mitochondria could play an important role of external proofreader in removing nucleoside analogs from the 3'-end of the DNA, thus reducing the toxicity of the NA's.

PP 2.29.

High Levels of HIV-1 Infection of CD8 Lymphocytes Expressing CD4 in vivo

Cochrane A, Leen C, Scott G, Simmonds P. University of Edinburgh, Edinburgh, UK

Introduction. Recent data has demonstrated that CD8 lymphocytes activated in vitro express cell surface CD4 (generating a CD8brightCD4dim phenotype) and can be infected by HIV-1. If CD8 lymphocytes responding to pathogens in vivo are similarly targets of HIV-1 infection, this could contribute to the decline in cytotoxic T lymphocyte function seen with progression to AIDS. In addition, data from the thy/hu mouse has demonstrated that lymphocyte precursors infected with HIV in the thymus can be exported into the periphery generating HIV infected long lived naïve lymphocytes which could act as treatment resistant HIV reservoirs.

The aim of this paper was to assess the frequency and phenotype of CD8brightCD4dim lymphocytes in HIV infected subjects and to determine whether these cells are HIV infected in vivo. In addition, the in vivo importance of export of intrathymically infected T lymphocytes was assessed.

Methods.

The prevalence and differentiation phenotype of CD8brightCD4dim lymphocytes in the blood of 13 HIV infected subjects with a range of HIV disease stages, was assessed by flow cytometry. In 9 of these subjects highly purified CD4 lymphocytes and CD8 lymphocyte subsets (CD8brightCD4dim and CD8+CD4-) were isolated by fluorescent activated cell sorting. The purity of isolated subsets was assessed by flow cytometry and the proviral load in terms of HIV proviral copies per 106 cells was quantified by real time PCR.

Results. Distinct CD8brightCD4dim lymphocyte populations were observed in all subjects. These cells contributed between 0.8 and 3.3% of the total circulating CD8 lymphocytes, with the majority displaying a memory phenotype (CD45RA-CD27+). The CD8brightCD4dim lymphocytes were found to be infected with HIV provirus in 7 out of the 9 subjects assessed and carried relatively high proviral loads (median 865 proviral copies per 106 cells), which were comparable to the proviral loads in CD4 lymphocytes from the same subjects (median 1830). In contrast HIV infection of CD8+CD4- lymphocytes was only demonstrated in 2 of 9 subjects and these carried very low proviral loads.

Discussion. This is the first study to quantify HIV infection of CD8brightCD4dim lymphocytes isolated from HIV infected subjects. The observation that proviral loads in CD8brightCD4dim lymphocytes are comparable to those in CD4 lymphocytes suggests a significant level of infection which may contribute to the defects in CD8 lymphocyte function observed with disease progression. The very low or undetectable levels of HIV provirus in CD8+CD4- lymphocytes suggests that export of intrathymically infected CD8 lymphocyte precursors occurs rarely if at all.

PP 2.30.

Evaluation of the Abbott LCx HCV-RNA Quantitative Assay

Ceccherini-Nelli L, Malizia T, Giannotti A, Vanni M, Lico S, Avena S, Moriconi F, Comastri G, Pulvirenti FR, Thamm S, Campa M.

Dipartimento di Patologia Sperimentale B.M.I.E., U.O. di Microbiologia Universitaria, AOUP, Pisa, Abbott Molecular Diagnostics, Roma, Italy; Abbott Molecular Diagnostics, Wiesbaden, Germany

Introduction. The increasing adoption of stopping therapy rules based on the decline of HCV-RNA pre-treatment levels at 12 weeks or earlier after therapy initiation, requires viral load assays able to couple a good precision with wide dynamic range and exquisite sensitivity. We evaluated the performance characteristics of the Abbott LCx HCV-RNA quantitative assay (stated dynamic range: 23-2,300,000 IU/mL), based on silica-membrane (QIAmp) extraction, competitive RT-PCR and automated amplicons detection by MEIA on the LCx analyzer (total time for 24/48 samples: 6/7 hours). **Methods** Accuracy, precision and linearity were verified with an Acrometrix panel (50; 500; 50,000; 500,000; 1,000,000 IU/mL), tested in reps of 4 for each level during 6 runs. Reproducibility was also assessed by the low and high positive kit controls (CP1 and CP2), required in singlicate in each run for validation purposes. 101 blood donors samples, anti-HCV and HCV-RNA negative, were tested for assay specificity. 210 retrospective routine samples tested with HCV-RNA COBAS Monitor were used for assay correlation. **Results.** Total CV (log IU/mL) for the panel ranged from 2.7% to 9.2%, showing value of 4.3% and 3.4% for CP1 and CP2 respectively. Linear regression line between LCx measured (y) and expected (x) values had the following equation: $y = 1.13x - 0.48$ (R^2 0.9966). LCx detection rate at 50 IU/mL was 52% (12/23), with 79% of the 1,000,000 reps within dynamic range. 99% (100/101) specificity was observed and the only initial reactive sample (26 UI/mL) was negative on repetition. 37 samples (17,6% of the total) with Monitor result above 500,000 IU/mL, gave a LCx value within dynamic range, with only 6 samples (2,8%) showing the opposite (>2,300,000 with LCx and within range with Monitor). 9 samples with Monitor results <600 UI/mL and positive with the qualitative test (HCV-RNA COBAS Amplicor), were measurable with LCx, showing a range of values (85-676 IU/mL), in agreement with undetectability by the Monitor assay. 74 results within range for both assays gave a correlation coefficient (linear regression) of 0.908. All samples differed for less than 1 log, with a LCx tendency to provide higher results for values greater than 5.5 log IU/mL. **Discussion.** The LCx HCV-RNA assay showed excellent precision and linearity, good specificity and correlated well with the test of reference. The wider LCx dynamic range translated into a 19% gain of reportable results (4% <600 UI/mL and 15% > 500,000 IU/mL) compared to the Monitor assay. Although based on conventional RT-PCR, the LCx HCV assay may represent an advancement in HCV-RNA monitoring, allowing the adoption of a single test for both qualitative and quantitative requests.

PP 2.31.

Comparison Among Three Different Systems Of Genotype Interpretation In HIV Resistance Testing

Setti M, Ventura A, Bruzzzone B, Nigro N, Demetri A, Caligiuri P, Cardinale F, Lai P.

Department of Internal Medicine, Department of Health Sciences, university of Genoa, Genoa, Italy

Due to feasibility and lower costs the use of genotypic versus phenotypic assays is constantly increasing in HIV infection management. The prediction of drug resistance on the bases of genotypic sequences requires expert interpretation, which currently relies on the use of specific algorithms. Those programs are based on data derived from several studies aimed to pair genotypic and phenotypic tests, in order to assign a certain pattern of resistance to a given genotype. However, the interpretation of those data may differ somehow according to the panel of experts involved, so that the results from different algorithms may bear discrepancies for the same genotype. To compare the impact of three of these tests in the choice of treatment protocols, the viral sequences from 57 patients in which resistance testing was requested to our laboratory were analysed by Trugene (Visible Genetics - VG), Stanford HIV-SEQ program (Stanford University data-base - SU) and Virtual Phenotype Analysis (Virco - VP). Complete concordance was found in only 5 out of the 57 (8.8%) tested samples: 3 wild type and 2 NNRTI resistant strains. Dissecting the data into the different classes of drugs, the following concordances were found: 11 (19.3%) for NRTI (all wild type for NRTI related mutations), 40 (70.2%) for NNRTI and 36 (63.2%) for PI. For NRTI class the major degree of discordance (over 50%) was found for ddI, ddC, d4T, TDF and ABC. When comparing VG with SU, discordance drops as low as 10% or less for ddI, ddC and d4T, if different grading of resistance is not taken into account, whereas it remains high for TDF (28%) and ABC (17.5%). When comparing VP with VG or SU, the levels of discrepancies stand over 50% for these five drugs. Overall discrepancies were lower for AZT (about 30% in every match), lowest for 3TC (about 12%, only 5% between VG and SU). For NNRTI concordance was much higher: 87.7% for NVP and 73.7% for EFV, with slight differences in the various matches. For PI class, overall concordance was about 82%, excluding APV and LPV which gave about 60% concordance in every match. In conclusion, the two pure genotypic tests (VG and SU) gave reliably concordant results for the majority of drugs, not considering the grading, except for TDF and ABC, with SU resulting somewhat less permissive than VG. The real phenotype-matched VP genotypic test gave a major number of discordances, particularly for the NRTI class. Overall, in accordance with literature, this test was more permissive compared with the other two when discrepancies were found. Although this might seem dangerous for a safe choice of drugs in a standard setting, in those scenarios with extremely poor options it could show unexpected opportunities.

PP 2.32.**Partial Resistance To HIV-1 Disease Progression Induced By SDF1 3'UTR A801G Polymorphism: A Molecular Explanation**

Rueda P, García-Moruja C, Torres MC, Alcamí J, Caruz C. Dpto. Biol. Exp.
Universidad de Jaén, Jaén, C.N.B.F. Instituto de Salud Carlos III, Madrid, Spain

Introduction: Stromal-cell derived factor (SDF1) is a CXC-type chemokine that binds specifically and exclusively to CXCR4. SDF1 is essential for B lymphopoiesis, myelopoiesis, cardiac ventricular septal formation and it has chemotactic activities on lymphocytes and monocytes. Also SDF1 has antiviral activity against X4 dependent HIV strains by inducing HIV co-receptor endocytosis. A polymorphism located in the 3' untranslated region (UTR) of SDF1 mRNA is associated to partial resistance to HIV-1 disease progression. But the precise effects of this polymorphism on mRNA or protein production has not been previously demonstrated. **Methods:** Using a SDF1 β promoter+luciferase plasmid, we have cloned the untranslated regions of SDF1 β , wild type SDF1 β and mutant SDF1 β , at the 3' end of the luciferase gene. Transfection by electroporation of astrocytes (U373) and embryonic lung fibroblast (LC5). Treatment 24 horas post-transfection by a series of different stimuli. Luciferase activity measurement, 24 h post-treatment.

Results: % induction compared to promoter SDF1 unstimulated:

CONSTRUCT	Unstimulated		Interferon γ		PMA+ Ionomycin	
	LC5	U373	LC5	U373	LC5	U373
Promoter + luciferase	100	100	117	69	1059	210
Promoter + luciferase+ UTRa	66	491	62	595	901	2019
Promoter + luciferase + UTRb wt	162	60	126	65	1013	184
Promoter + luciferase + UTRb mutant	318	701	203	679	2290	848

Discussion: The most striking finding is difference between expression patterns of mutant and wild type UTR β . The mutation increases significantly the luciferase activity and the effect is more prominent in astrocytes compared to fibroblast. These results suggest that the mutation G801A at the 3'UTR of SDF1 induces a higher mRNA stability, higher protein expression and probably a better CXCR4 endocytosis. These observations contribute to explain at the molecular level the resistance phenotype to HIV infection shown by patients with the G801A mutation.

PP 2.33.

Carraguard* Prevents Macrophage Trafficking from Vagina: implications for microbicide development

Perotti ME, Pirovano A, Phillips D.

University of Milan, Italy; Population Council, New York, USA

Considerable evidence suggests that HIV infected macrophages and/or lymphocytes may mediate sexual transmission of HIV. Our laboratory and other laboratories have previously demonstrated that when vitally stained donor mouse lymphocytes or macrophages are placed in the vaginas of mice, some of the stained cells can later be found in the iliac lymph nodes. The aim of this study was to assess the extent of mononuclear cells trafficking from the vagina and to test the possibility that Carraguard™ (PC-515), a vaginal microbicide, would prevent vaginal transmigration of macrophages. When we inoculated mouse mononuclear cells with supravitaly stained macrophages; Carraguard™ reduced the number of macrophages in lymph nodes and the spleen by greater than 90%. In contrast, the placebo formulation reduced the number of vitally stained macrophages in the lymph nodes by only 50%. Both formulations were minimally toxic to macrophages over a 1-hour period as compared to no treatment, whereas they were not toxic to human cervical cells. Our findings suggest that Carraguard™ blocks cell trafficking of macrophages from the vaginal vault. Blocking does not appear to result from cytotoxicity. We speculate that blocking cell trafficking may help to prevent sexual transmission of HIV.

PP 2.34.**Human Immunodeficiency Virus Transactivator Protein (Tat) Induces a Calcium Increase Through L-type calcium channels of Human Monocytes**

Contréras X, Bennasser Y, Chazal N, Moreau M, Leclerc C, Bahraoui E.

Laboratoire

d'immuno-virologie, Centre Biologie développement, Université Paul SABATIER, Toulouse, France

Introduction : In addition to the depletion of TCD4 lymphocytes, HIV-1 induces an immunodepression, since the asymptomatic stage, associated mainly with the alteration of the Th1/Th2 balance of cytokines, including TNF α , IL-1, IL-4, IL-6, IL-10 and IL-12. HIV-1 Tat protein, by acting at the cell membrane level, stimulates in human monocytes both TNF-alpha and IL-10. The objective of this study was to characterize the source of the calcium mobilization following stimulation by HIV-1 Tat in human monocytes and to analyze the mechanisms involved.

Methods : Human primary monocytes isolated from HIV-seronegative healthy blood donors on a ficoll density gradient were stimulated by recombinant HIV-1 Tat protein (10nM). Calcium signaling was assessed by videomicroscopy using the calcium fluorescent probe fluo3-AM. The study of the presence and functionality of L-type calcium channels on monocytes included confocal microscopy using DHP-bodipy as probe. TNF-alpha and IL-10 producing cells were determined by FACS analysis.

Results : In this study, we show that Tat protein, through its aa20-45 region, induces a calcium increase in human monocytes. The mobilized calcium seems to have rather an extracellular origin since i) no signal was observed when monocytes were stimulated in a calcium free medium, ii) the calcium increase was not affected when stimulation by Tat was performed in the presence of Xestospongine C or TMB8, two inhibitors of intracellular stores. To investigate the presence of L-Type calcium channels, we used a variety of complementary approaches including specific antisense oligonucleotides for these channels, RT-PCR and western blot specific of the $\alpha 1$ subunit. These channels seem to be functional as assessed by the use of the agonist of L-type calcium channels BayK8644-. Nimodipin, calcicludin and antisense oligonucleotides for L-type calcium channels, are able to inhibit the calcium increase induced by Tat. Moreover, we showed that both IL-10 and TNF-alpha productions are calcium dependent.

Conclusion : Altogether, these results strongly suggest that Tat, through its aa20-45 region, stimulates L-type calcium channels on monocytes to induce a calcium increase which may be involved in TNF-alpha or IL-10 production.

PP 2.35.

HIV-1 Tat Directly Binds To NF κ B Enhancer Sequence: Role In Viral And Cellular Gene Expression

Dandekar DH, Mitra D, Ganesh KN.

Organic Chemistry Synthesis, National Chemical Laboratory, National Centre for Cell Science, Pune, India

Introduction: Tat protein, of Human Immunodeficiency Virus-1 (HIV-1), activates long terminal repeat (LTR) promoter directed transcription by interacting with transactivation response region (TAR). In addition, several studies have shown convincing evidences that Tat can transactivate HIV-1 gene expression in absence of TAR but the molecular basis of this activation remains to be clearly understood. A number of earlier studies indicate that Tat could substantially effect transcription when artificially tethered to DNA, but cognate target for native Tat remained to be identified. In current study we investigated the binding of Tat protein with upstream enhancer sequences from HIV-1 LTR which have important role in TAR independent transactivation.

Methods: Gel shift assay, SELEX, transfection studies for reporter constructs, and Chromatin immunoprecipitation studies were used to investigate the direct interaction Tat protein with DNA

Results: The present study demonstrates Tat could interact with DNA, specifically with upstream NF κ B enhancer sequences in LTR, which has been shown to be important for both TAR independent and dependent Tat responsive transactivation of HIV-1 LTR.

Discussion: Tat regulation of LTR mediated gene expression by binding to NF κ B enhancer sequences points toward a novel regulatory mechanism for viral gene expression. Also, Tat binding specifically to chromatin enhancer sequence elements assumes significance not only towards solving paradox of TAR independent transactivation of HIV-1 LTR but also the modulation of several other cellular gene promoters. (Dandekar, D. H., Ganesh, K. N., and Mitra, D. (2004) *Nucleic Acids Res.* 32 (4), 1270 -1278.)

PP 2.36.

Molecular Mechanism of Methionine-enkephalin on the Suppression of SIV infected Lymphocyte Apoptosis

Li P, Liu X, Li G, Xu J.

Department of biochemistry and molecular biology, Peking University, Beijing, China

Methionine-enkephalin(MENK) is a sort of cytokine which has the function of regulating the human immune system. To investigate the effect of MENK on the apoptosis of SIV (Simian Immunodeficiency virus) infected cells, our research use CEM x174 cells infected with SIV as a model. We have made primary studies about the mechanism of MENK on cell apoptosis. Florescent staining Hoechst 33258 was incubated with SIV infected cells and cell morphology was observed under microscope ; DNA fragmentation assays were detected by agarose gel electrophoresis; And Annexin-V staining for phosphatidyl serine(PS) externalization was analyzed by flow cytometry (FCM). Our results demonstrated that SIV can induce CEMx174 cell apoptosis. When treated with 1 μ M MENK, 72 hours later, SIV infected CEMx174 cells were detected by MTT assay. No obvious effect can be found on the viability of infected cells. FCM analysis showed that MENK didn't function on the externalization of PS. Nevertheless, by investigating the expression of cell apoptosis regulatory proteins, we observed that MENK can enhance bcl-2 expression of late stage SIV infected cells, and reduce P53, caspase-3, bax expression. Opioid receptor blocking reagent Naloxone can inhibit such function. By means of RT-PCR detection, it indicated that MENK attenuated the expression of TNF- β , an apoptosis cytokine in correlation with early stage SIV infected cells. We conclude that MENK can suppress the apoptosis of SIV infected CEMx174 cells through the mediation of opioid receptor. Cell death gene proteins such as bcl-2, P53, caspase-3 and bax might have played an important role in the suppression mechanism.

PP 2.37.

A Rationally Designed CD4 Miniprotein, Useful to Discover Specific Ligands of HIV-1 GP120 Glycoprotein

Stricher F, Martin L, Mechulam A, Mons S, Barthe P, Roumestand C, Ménez A, Veas F, Vita C. Département d'Ingénierie et d'Etudes des Protéines, CEA Saclay, Gif-sur-Yvette, Laboratoire d'Immunologie Rétrovirale et Moléculaire, IRD/CNRS, Centre de Biochimie Structurale, Université de Montpellier, Montpellier, France

Using structural information on CD4-gp120-17b complex, we designed a 27 amino acid miniprotein, CD4M33, which reproduces the hot spot of CD4 surface binding gp120, presents optimal interaction with gp120 and binds HIV-1 particles and diverse viral envelopes. CD4M33 inhibits infection of primary isolates and induces gp120 conformational changes that expose conserved cryptic epitopes, thus it is a small-size fully functional CD4 substitute. CD4M33 was labelled with fluorescein and used in polarisation assays to study binding to a panel of HIV-1 envelope glycoproteins in solution. Nanomolar equilibrium dissociation constants were determined, which reflect CD4-like affinity for HIV-1 envelopes. CD4M33 contains a biphenylalanine (Bip)-23 residue, which is equivalent to CD4 Phe-43 and, in a CD4M33-gp120 computed complex, engages the gp120 "Phe-43 cavity". To better understand how CD4M33 binds gp120 structure, we synthesized a CD4M33F23 mutant, which contains a shorter Phe-23 side chain, and a gp120S375W mutant, which contains the "Phe-43 cavity" filled. ELISA or Biacore experiments showed that CD4M33 could bind gp120S375W with thousand-fold reduced affinity, while CD4M33F23 bound with nanomolar affinity, thus demonstrating that the Bip-23 side chain of CD4M33 engages the "Phe-43 cavity". Thus, fluorescent CD4M33 or CD4M33F23 can be used to distinguish molecules that can bind to the CD4 binding site or "Phe-43 cavity" of HIV-1 envelope glycoproteins. By using fluorescent CD4M33 as tracer in competition assays and 384-well microplate format, a sensitive fluorescent polarization assay was set up and used to determine dissociation constants of a variety of gp120 ligands. This assay is routinely performed in 20 µL volume and also amenable to further miniaturization. Interestingly, in our assay, BMS-378806, originally proposed to bind gp120 to the CD4 binding site, was shown not to bind to this site, in agreement with more recent studies.

PP 2.38.**Morphine stimulate apoptosis of SIV infected CEM x174 cells**

Xu J , Li PF, Liu XH, Li G.

Department of biochemistry and molecular biology, Peking University, Heath Science Center, Beijing 100083, China

The consisting exhaustion of CD4+T cells plays a significant role in the deficiency of the immun system of AIDS patients. While lymphocyte depletion as a result of apoptosis is one of the important features of CD4+T cells exhaustion. The correlation of opioids and HIV infection has been well established. Intravenous drug abuse is an important factor to stimulate HIV replication and dissemination. Opioids change the process of AIDS by affecting the function of the immune system of the patients. As a result, it is of great significance to demonstrate the effect of opioids on the apoptosis of HIV infected cells. Our research use CEMx174 cells infected with Simian immunodeficiency virus (SIV) as HIV infection model to investigate the effect of Morphine on the apoptosis of SIV infected cells. The infected cells were observed under microscope after Hoechst 33258 staining. DNA ladders were detected by agarose gel electrophoresis, and phosphatidyl serine (PS) externalization was analyzed by flow cytometry (FCM). Our results showed that SIV infection can cause apoptosis of CEM x174 cells. 1 μ M Morphine was added to HIV infected CEM x174 cells. After 72 hours incubation, we observed that Morphine can attenuate the viability of infected cells by MTT assay; Annexin-V staining by FCM showed that Morphine stimulated the apoptosis of late stage infected cells; Western blotting was employed to detect the alteration of cell apoptosis regulatory proteins of SIV infected cells 72 hours after treated with Morphine. The expression of P53, caspase-3 and bax were promoted, and expression of bcl-2 was decreased. Nevertheless, Naloxone, opioid receptor blocking reagent can inhibit the function of Morphine. What's more intriguing is that we found Morphine can reduce expression of TNF- β in early stage SIV infected cells by means of RT-PCR method.

We conclude that Morphine can stimulate apoptosis of late stage SIV infected CEM x174 cells mediated by opioid receptor. And cell death gene proteins such as P53, caspase-3, bax, bcl-2 and so on play important roles in the process.

PP 2.39.

Different Characteristics of HCV-specific CD8+ T Cell Responses in Chronic HCV Infection, HIV Coinfection and Spontaneous Clearance

Barrett L, Howley C, Hirsch G, Peltekian K, Bowmer MI, Grant M.

Memorial University of Newfoundland, St. John's, St. John's Health Care Corporation, Dalhousie University, Halifax, Canada

Introduction: While strong T cell responses are associated with clearance of acute HCV infection, the role of CD8+ T cell responses in chronic HCV infection and HIV/HCV coinfection is unclear. HIV-infected individuals coinfecting with Hepatitis C virus (HCV) often have accelerated liver disease, which could relate to more prominent CD8+ T cell activation. Our objective was to compare the specificity, breadth and magnitude of HCV-specific CD8+ T cell responses in HIV/HCV coinfection, chronic HCV infection, and in cases of spontaneous clearance.

Methods: Three groups were studied: HIV/HCV coinfecting individuals (n=11); individuals with chronic HCV infection (n=18); and individuals who spontaneously cleared HCV infection (n=5). To evaluate HCV-specific CD8+ T cell responses, peripheral blood mononuclear cells (PBMC) were stimulated for 24 hours with 44 pools of 15-mer peptides spanning the entire HCV-1a genome. The number of HCV-specific interferon-gamma (IFN- γ)-producing cells per million PBMC was estimated by ELISPOT.

Results: The proportion of individuals with HCV-specific CD8+ T cell responses was similar in HIV/HCV coinfecting, HCV-monoinfected and spontaneous clearance groups (85%, 90% and 100% respectively). Response breadth was greatest in the spontaneous clearance group. Although the breadth of HCV-specific responses was lowest in the HIV/HCV coinfecting group, the overall magnitude was greatest compared to chronic monoinfection and spontaneous clearance (839 spot forming units (SFU)/million PBMC versus 230 and 269 SFU/million PBMC, respectively; $p < 0.01$). HCV core, non-structural protein 4A (NS4A) and NS4B derived peptides were most commonly recognized in all groups. Recognition of NS3 peptides was common only in the HIV/HCV coinfecting and spontaneous clearance groups, not in chronic monoinfection. NS2 peptide recognition was common in HCV monoinfection and spontaneous clearance but not in the context of HIV coinfection.

Conclusions: HIV coinfection is associated with stronger, but more narrowly directed, HCV-specific CD8+ T cell responses. There is similarity between all groups in the regions producing frequent responses however there are some clear differences. Narrow responses with greater strength and altered specificity may play a role in the accelerated disease course of HCV in HIV coinfection.

PP 3.1.

The Value of PCR HIV RNA for Early Detection of HIV Infection

Pesic I, Zerjav S.

CCS-Institute for Infectious and Tropical Diseases - Virology Department, Belgrade, Serbia & Montenegro

Objective: To evaluate the correlation of ELISA, WB and PCR HIV RNA in early detection of acute HIV infection.

Materials and methods: Sera samples of four patients with acute febrile infection and generalised lymphadenopathy, all male, two of them were homosexuals and two of them drug abusers. Sera samples were taken every 5-7 days.

The tests that we used were different ELISA (Dade-BEHRING, Murex, Biorad), WB (Biorad, Liatek) and Amplicor PCR HIV RNA (Roche).

Results: In the first sera samples all patients were ELISA negative and no antibodies were detectable by WB. PCR HIV RNA were 4,5 to 6,20 log₁₀. In sera samples taken after 7-10 days ELISA tests became positive and antibodies for p17, gp41/gp120 by WB were detectable. In the meantime HIV RNA usually increased up to over 6,20 log₁₀.

In sera samples taken after 10-20 days, along with positive ELISA, almost all antibodies were detectable by WB (except antibodies to enzymes) while HIV RNA decreased rapidly from 10 to 1000 fold.

Conclusions: Besides the significance of HIV RNA for therapy monitoring and disease progression, it could be very useful for early diagnosis of HIV infection and seroconversion. It could be successfully used in adults instead of the detection of HIV DNA.

PP 3.2.

Management of HIV/TB coinfection in Cuba

Díaz Jidy M, González Nuñez I, Pérez Avila J.

Institute Pedro Kouri Autopista Novia del Medio Dia, La Haban, Habana, Cuba

Background: Diagnosis of the HIV/TB association poses new difficulties because of the atypical manifestation of the disease. Besides, its treatment interferes with the antiviral drugs, mainly with protease inhibitors (PI). This paper reports on our experience in the diagnosis and treatment of HIV-associated tuberculosis.

Method: All the medical records of HIV/TB coinfecting patients hospitalized at the IPK hospital, during the year 2002 and 2003, were reviewed.

Results: In Cuba, from the onset of the AIDS epidemic in 1986 to December 31, 2003, 5,257 positive cases have been reported: 4,171 male and 1,086 female. At IPK, during 2002 and 2003, 61 patients have been diagnosed with HIV/TB coinfection: 46 male and 21 female. Twenty-four of them had bacteriological and 37 did not but showed strong clinical, epidemiological and laboratory evidences. The latter were daily treated with rifampin, isoniazid, ethambutol and pyrazinamide for 60 days, followed by 40 doses, twice a week, of isoniazid and rifampicin. Previously, all the non-indispensables drugs had been discontinued and treatment was started including a different drug each day in order to detect adverse reactions and to find out which of the drugs could cause such undesirable reactions.

Antiretroviral treatment scheme was as follows: if clinical debut of both diseases was simultaneous and the patient showed more than 350 CD4/ml, only treatment for TB was ordered. If CD4/ml value was lesser than 350, antiretroviral treatment with protease inhibitors (PI) was started. If patient status was deteriorated or had previous treatment with protease inhibitors, rifampin was replaced by rifabutin and doses of PI were adjusted.

Conclusions: Diagnosis of tuberculosis in AIDS patients is very difficult because of the atypical presentation of this disease and of the existing problem related to the combined treatment of antituberculous and antiviral drugs used.

PP 3.3. BCG skin reaction in Mantoux-negative Healthy Children

Goyal HK, Singla M, Gupta RP.
Government Medical College, Patiala, India

Introduction :

The treatment of this epidemic disease puts a real challenge especially in Children. This study has been carried out to determine the pattern of BCG reaction comparing previously vaccinated with non-vaccinated children .

The response of BCG may be different in previously vaccinated children and needs to be considered before interpreting positivity for TB . This study has been carried out to determine the pattern of BCG reaction comparing previously vaccinated with non-vaccinated children.

Methods :

The study was conducted in the healthy school children aged 4-6 years . The comparison was done between the BCG skin reaction in Mantoux-negative children previously vaccinated with BCG, evidenced by scar, and the reaction between children with and without previous BCG scar. After the Mantoux and BCG test the analysis of variance (ANOVA) was done as per protocol

Results :

Out of 50 children in children who were given prior BCG vaccination , 39 had exaggerated BCG test responses while children who were not given prior BCG vaccine only 9 out of 50 cases had exaggerated BCG test response. Average induration obtained in children who were immunized with BCG at birth was much greater than those who were not immunized . 80% and 76% males and females respectively in group I showed exaggerated BCG response while 16% and 20% males and females respectively of group II showed exaggerated BCG response .

Discussion :

The present study indicates that normal healthy children may have a mild exaggerated BCG test response i.e. induration up to 8 mm because of prior BCG vaccination. Therefore, the patients, immunized with BCG at birth in whom other parameters for diagnosis of tuberculosis are not suggestive, may continue to receive unnecessary anti-tubercular therapy. BCG test, though important should not be the only criteria for start of chemotherapy for TB in children as the side effects of drugs put a major challenge An induration up to 8 mm after the BCG test can be normal in Indian settings due to exposure to Mycobacterium in environment and/or BCG vaccine .

PP 3.4. Severe Herpes Zoster in Apparently Healthy African Adults: a marker for HIV seropositivity

Onayemi O, Oninla O. A.

Department of Dermatology & Venereology, Faculty of Clinical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria

These case reports suggest a possible relationship between severe herpes zoster in apparently healthy African patients and seropositivity for human immunodeficiency virus. Any patient with herpes zoster accompanied by marked cutaneous tissue damage should be encouraged to undergo HIV/AIDS screening even if the patient has no other risk factor for acquiring HIV/AIDS. A positive result would allow the early institution of appropriate dosage of acyclovir treatment and the proper counselling of the patient on the course of HIV/AIDS.

PP 3.5.**Acute HCV In A Cohort Of HIV-positive Men - Outcomes And Response To Pegylated Interferon-alpha 2b And Ribavirin**

Bhagani S, Danta M, Fernandez T, Slapak G, Dusheiko G, Johnson MA .Royal Free Hospital London, UK

Background: An epidemic of acute HCV has recently been recognised amongst HIV-positive men in London. We describe virological outcomes and initial response to early treatment in our cohort.

Definitions: Acute HCV was defined as a documented negative HCV antibody test (EIA-3) in the 6 months prior to a positive antibody test and/or a positive HCV-RNA by RT-PCR determined by TMA testing. HCV RNA was determined monthly initially. Patients with two consecutive HCV RNAs < 50 copies/ml at least 4 weeks apart were designated spontaneous clearers. All other patients were offered immediate treatment.

Treatment protocol: All patients with a persistently positive HCV RNA by RT-PCR twelve weeks after presentation were offered PegIFN-alpha 2b (1.5 µg/kg) and ribavirin (>10.6 mg/kg) for 48 weeks.

Results: Since October 2002, 36 cases of acute HCV have been identified (mean age 30.5 years, median CD4 514 cells/µl). 17 were on HAART. Genotype 1 infection was noted in 21(58%), genotype 3 in 7 (19%), genotype 4 in 4 (11%) and 4 were un-typable. 9 (25%) have spontaneously cleared HCV. Median follow-up of this group is 32 weeks. Treatment has been started in 16 patients (median CD4 514 cells/µl, median HCV viral load (vl) 5.86 logs, 12 genotype 1, 3 genotype 3, 1 genotype 4). At week 12, of the 15 patients evaluated, 11 (73%) have achieved an early virological response (HCV vl <50 iu/l or > 2 log decrease), 2 are non-responders, 1 has stopped therapy due to intolerance and 1 patient has been lost to follow-up. Of the 9 patients followed through to week 24, 6 (66%) have an undetectable HCV-RNA, 2 remain non-responders and 1 stopped. 2 patients stopped therapy between 24-48 weeks and remain undetectable. At week 48, 3 patients have achieved end of therapy response and 2 are non-responders.

Conclusions: Spontaneous clearance of HCV is possible despite HIV co-infection. Initial results suggest a favourable response to early treatment despite unfavourable genotypes and high HCV viral loads.

PP 3.6.

Gynecomastia in an Adolescent with Perinatal HIV Infection: associated variables

Manfredi R, Calza L, Chiod Fo.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

Gynecomastia is an emerging untoward event of antiretroviral-treated HIV disease. Although initially related to HIV protease inhibitors and dysmetabolism, it has been recently reported in patients who never received (or abandoned) protease inhibitors. Among nucleoside analogues, stavudine seems the most frequently implicated molecule, although biases due to its large-scale use cannot be excluded. A perinatally HIV-infected boy at the age of 13.5 years developed a true, ulyrasonography-confirmed bilateral gynecomastia, responsible for mild paresthesia and local discomfort. At the time of onset of gynecomastia, an endocrinological workout did not disclose any gonadal, hypophyseal, thyroid, and prolactin abnormality. Chronic liver and/or kidney failure, and administration of drugs potentially related to gynecomastia, were carefully ruled out. Height and weight development milestones and pubertal stage were within normal limits, according to patient's age. At the age of five our patient started antiretroviral therapy due to a peak of viremia, and never stopped treatment thereafter. During the 9-year subsequent follow-up, five therapeutic lines were used, including HAART regimens based on different protease inhibitors. When considering nucleoside analogues, stavudine was the compound administered for a longer time (61 months). When gynecomastia was diagnosed, a negligible viremia was retrieved (280 HIV-RNA copies/mL), while CD4+ lymphocyte count was 848 cells/ μ L. Our patient never presented lipodystrophy-defining alterations, and no metabolic abnormality was detected through the entire follow-up period. Gynecomastia did not show modifications during the 9 months of observation. In conclusion, among the over 100 reports of HIV-associated gynecomastia described until now, none emerged in pediatric and/or adolescent age. Both pathogenesis and evolution of gynecomastia are increasingly investigated, with attention focused on dysmetabolic alterations and lipodystrophy (absent in the presented case), as well as single antiretroviral agents and their combinations. In the described patient, nucleoside analogues and protease inhibitors were given during 8.5 and 7 years, respectively. In our patient, who represents the first case of true gynecomastia in a child, the absence of lipodystrophy and/or dysmetabolic alterations, makes uncertain the possible underlying etiopathogenetic pathways.

PP 3.7.

20 years Survey of HIV-related Malignancies in Alsace

Plaisance N, Lang JM, Beck-Wirth G, Chartier C, Hansmann Y, Michel C, Audhuy B.
Hôpitaux Civils de Colmar; Hôpitaux Universitaires de Strasbourg ; CH de Mulhouse, France

Background: early in the AIDS epidemic it was estimated that up to 36% of patients develop a malignancy during the course of their disease. We were interested in the incidence of AIDS- (Kaposi's Sarcoma, non-Hodgkin's Lymphoma and invasive cervical cancer) and non AIDS- defining cancers through the following years in these population, and in there influence since 1996 by the use of HAARTs, which has improved the survival of these patients.

Methods : all HIV related malignancies diagnosed in the Principal hospitals in Alsace were prospectively registered since 1984. Anonymous demographic and histological data were transmitted by involved physicians to the regional CISIH (Centre d' informations et de soins de l'immunodéficience humaine).

Results : between 1984 and 2003, 290 cases of HIV related malignancies were registered in Alsace, 170 between 1990 and 1996 (period I: without HAART) and 83 between 1997 and 2003 (period 2 : with HAART). KS represents 42 % of all tumours : 89 cases in period 1, 12 cases in period 2 , representing now only 14.5% off all malignancies instead of 52% previously. NHL and Hodgkin disease (74 and 10 cases) representing 26% of the total: 44 in period 1, 12 in period 2, but with a trend towards a relative increase in their rate(26 to 29%). Sixty Squamous cell carcinomas are 21 % off all tumours (more than 50 % are lo Situ Cervical Cancer) with an increase of 16 to 37% between the two periods. Other carcinomas (24 cases representing 8% of the total) are 9 in period 1, 12 in period 2, so their registration seems stable.

Conclusion: the dramatic fall of HIV related malignancies (around 50%) since the introduction of HAARTs represents the main epidemiological modification observed in Alsace since 1984. Nevertheless, Kaposi's sarcoma appears to be the most affected, whereas the occurrence of NHL decrease in a lower proportion and that of carcinomas seems at least stable.

PP 3.8.

Acquired Immunodeficiency Syndrome (AIDS) and Multiple Neoplastic Malignancies as Emerging Conditions in the Era of Highly Active Antiretroviral Therapy (HAART)

Manfredi R, Calza L, Chiodo F.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

The introduction of highly active antiretroviral therapy (HAART) determined a significant drop of AIDS-related opportunistic disorders, but it did not act on a series of HIV-associated neoplasms other than Kaposi's sarcoma. Aim of our study is to describe three rare cases of dual associated cancers occurred in HAART-treated patients, through a survey of 768 AIDS patients observed since 1985. Dual neoplasms never occurred in our series before the year 2000. Three male patients aged 35-55 years, with HIV infection detected five to ten years before, and treated with combination antiretroviral therapy (HAART), developed Kaposi's sarcoma followed by non-Hodgkin's lymphoma 8-11 months later in the first two cases, while the third patient had a bladder carcinoma followed by non-Hodgkin' lymphoma 15 months later. Their clinical and laboratory response to antiretroviral therapy was limited by frequent virologic rebounds and maintained, low-level HIV replication, and a persisting CD4+ lymphocyte depletion (70 to 350 cells/ μ L through the entire study period). Despite a slowly progressive course of Kaposi's sarcoma obtained by cytotoxic treatment, the occurrence of a highly malignant non-Hodgkin's lymphoma led to death the first two patients, 5-11 months after diagnosis, notwithstanding multiple attempts performed with different chemotherapy regimens. The third patient underwent repeated local treatments for bladder carcinoma, and received six consecutive MACOP-B cycles for non-Hodgkin's lymphoma, and still survives despite concurrent development of neutropenia and opportunistic infections. In conclusion, despite the prolonged life expectancy following the introduction of HAART into clinical practice in mid-1996, immune dysregulation and co-infections with potentially oncogenic viruses, prompt a broadened spectrum of HIV-associated neoplasms, even compared with the pre-HAART era. This phenomenon remains underestimated, since only a few malignancies are included among AIDS-defining disorders, and those occurring after AIDS diagnosis are not reported by current national registries. However, dual HIV-related cancer remains a very rare occurrence, reported only once by the international literature, to the best of our knowledge. Health care givers should maintain an elevated clinical suspicion for a second malignancy, when facing HIV-infected patients already diagnosed with cancer. Strict epidemiological and clinical monitoring are strongly needed, in order to give a reliable estimate of the incidence and mode of presentation and evolution of this emerging HIV-associated malignant disorders.

PP 3.9. Cardiac Tumor in an HIV-1 Patient

Comenda E, Cardoso O, Goncalves P, Machado J, Maltez F, Mourao L.
Hospital de Curry Cabral, Lisboa, Portugal

The authors present the case of a 24-year-old male, drug addict in the past, admitted with syncope, substernal pain, dyspnea, fatigue and a loss of 10 Kg in the last 2 months.

He had a grade 2 systolic murmur and hepatomegaly. The lungs were clear. The peripheral pulses were preselit and equal and there was no peripheral edema, nor lymphadenopathy or fever.

Analytically relevant data: Hematocrit-39%, white cells (per mm³)-10450, neutrophils-29,5%, lymphocytes-66,8%, platelets (per mm³)-277000, lactate dehydrogenase (U/liter)-1013. HIV serology was positive, with a viral load > 500000 copies of RNA per millilitre (log > 5.69) His CD4 lymphocyte count was 139 cells / mm³.

An electrocardiogram revealed: normal rhythm at a rate of 98 beats per minute, pulmonary P waves and Rr' wave in lead V1. The Chest X-ray revealed cardiomegaly.

A cardiac ultasonographic examination showed multilobular mass in the right atrium with invasion of the tricuspid annulus, mild tricuspid insufficiency and moderate pericardial effusion. The patient was submitted to cardiac surgery with removal of cardiac mass.

Histological examination showed cardiac tissue replaced by a dense infiltrate of large, atypical lymphoid cells - Diffuse Large-B-Cell Lymphoma of the heart.

The patient started highly active antiretroviral therapy (HAART) and chemotherapy which are being well tolerated.

Primary Cardiac Lymphoma (PCL) is defined as an aggressive B cell lymphoma that predominantly involves the heart and most frequently the right atrium (although it may involve other sites as well), being encountered in 3% of patients with AIDS.

The differential diagnosis of a right atrial mass can be difficult in these patients, but with the advent of HAART, the outlook for such patients may be optimistic.

PP 3.10.

Vasculitic Neuropathy in HIV Infection

Minijagap P, Jahathesan K. M.G.R Medical University, Chennai, India

Vasculitis causing peripheral neuropathy may be the first sign of HIV infection. We report four such cases in whom the onset of peripheral neuropathy led to the detection of HIV infection. Two patients presented with features of mononeuritis multiplex, while the other two had a lumbosacral polyradiculopathy. A prior history of blood transfusion was forthcoming in one of the patients. Sural nerve biopsies in all the four cases and the muscle biopsy in two, histologically showed evidence of vasculitis. Immunohistochemically, the viral antigen was not demonstrable in any of the biopsies, but on electron microscope, virus-like particles were identifiable in the Schwann cell cytoplasm and the perivascular macrophages in one case. To the best of our knowledge, this is the only report that has documented the virus in the Schwann cells as well as the perivascular macrophages lending credence to the fact that these viruses are neurotropic as well as lymphotropic. Immunoglobulin deposits were not demonstrable in any of the cases, suggesting that direct viral invasion may have a role in the pathogenesis of peripheral nerve vasculitis.

PP 3.11.

Cognitive Impairment in HIV Patients under HAART : neurophysiological and neurometabolic evaluation

Poizot-Martin I, Blanquet F, Frixon-Marin V, Michotey P, Drogoul MP, Gastaut JA, Planche D, Vion-Dury J. Service de Neurophysiologie, Hôpital de la Conception, CISIH, Hôpital Ste Marguerite, IRM, Hôpital Ambroise Paré, Service de Neurophysiologie, Hopital de la Timone, et Institut des Neusociences Cognitives de la Méditerranée (INCM UMR CNRS 6193, Marseille, France

About 20-40% of HIV patients under HAART display cognitive troubles. We have evaluated such patients using a) brain proton magnetic resonance imaging and spectroscopy (MRI/MRS), b) neurophysiology including both P300 cognitive evoked potential and EEG.

10 subjects (8 males and 2 females) with minor cognitive signs have benefited of MRI/ MRS single voxel examination (PRESS sequence, TE 135 ms, TR 1500). Four spectra were recorded from white matter (WM). NAA/Cho, NAA/Cr and Cho/Cr metabolic ratios were analyzed. P300 evoked potential were recorded in 9 patients using an acoustic oddball paradigm, just before EEG (recorded in 8 patients).

MRI is normal in 4/10 patients. Non specific WM abnormalities are detected in 2 patients and a cortical or sub-cortical atrophy in 5 patients. MRS is abnormal (2 of 4 recorded spectra with one abnormal metabolic ratio) in 8 patients, and normal in only 2/10 patients. EEG is abnormal in all patients (mainly with frontal or diffuse slow waves with sometimes more sharp waves, without spikes). P300 are normal in 5/9 patients, since the age-matched P3B latency was increased in 4/9. All the patients with an abnormal P300 display an abnormal EEG. The cognitive (P300) anomalies are found mainly in patients with high plasmatic viral load and low CD4 count.

Cognitive troubles in HIV patients under tritherapy are accompanied by: a) very frequent significant abnormal brain metabolism. These anomalies occur in presence of discrete MRI lesions eliminating any HIV encephalopathy with diffuse white matter lesions, b) a very frequent and non specific modification of cortical electrogenesis (EEG) and c) frequent abnormal cognitive P300 evoked potentials. Cognitive troubles of such patients are clearly from an organic origin.

The viral and/or iatrogenic origin of such abnormalities is still unknown.

PP 3.12.

The Epidemiology of the Cryptococcosis within the Sick VIH (Hospital point G) in 2002

Alassane Oumar A.A.O , Dao S, Doumbo OK, Diallo M, Diallo A, Poudiougou. PB.
Faculté Medecine, Pharmacie, Bamako, Mali

After a recall on the epidemiological knowledge on parasitoses and mycoses we expose our methodology and our results.

To the Total, 55 for the direct exam and the coloration to ink of dyes for the research of cryptocoques at patients Hospitalized during the period of the investigation.

Our results are next one:

The other interferences intestinal opportunists:

18 positive cases for the coloration of Henricksen are a prevalence of 4,24% for *Cryptosporidium* sps and 0,5% for *Isospora belli*
the technique of BAERMAN 8,7% the prevalence of *S. stercoralis*

For mycoses 30,9% the prevalence of *Cryptococcus neoformans*, 47,3% at the confirmed AIDS patients

Key words: Infections parasitaires, opportunist mycoses

PP 3.13.

Multiple Subcutaneous Lipomas during HIV Disease: which relationship with antiretroviral therapy and dysmetabolism?

Manfredi R, Calza L, Chiodo F.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

The so-called lipodystrophy syndrome and a broad spectrum of metabolic abnormalities, have emerged as a consequence of highly active antiretroviral therapy (HAART) administration. Fat increase may occur as central (visceral) adiposity, increased breast dimension, gynecomastia, lipomastia, as well as isolated local fat accumulation (i.e. "buffalo hump"). Eleven out of around 1000 subjects referring to our HIV outpatient centre (~1%) (9 males and 2 females, aged 36-58 years), experienced multiple ultrasonography-confirmed subcutaneous lipomas (3 to over 20 lesions), predominantly involving trunk and limbs, associated with mild-to-moderate local discomfort. Our patient series experienced 4-13 different antiretroviral lines: almost all available protease inhibitors and nucleoside analogues had been used previously or after the occurrence of lipomas, while a non-nucleoside reverse transcriptase inhibitor was used in one case only. At the time of lipoma onset, all patients were given a protease inhibitor-based HAART since 17-58 (mean 25.2 ± 13.1) months. Varied features of the lipodystrophy syndrome and concurrent dysmetabolism were present in patients who developed lipomatosis: a peripheral lipodystrophy was present in 9 cases out of 11, in association with visceral adiposity in four patients, while localized fat accumulations were never found. Hypertriglyceridemia, hypercholesterolemia, and hyperglycemia were detected in 8, four, and one patient of 11, respectively. All patients in our series had a favorable clinical, immunological, and virological response to ongoing HAART. No patients had full-blown AIDS, and the duration of seropositivity varied between 38 and 121 months. Risk factors for HIV infection included i.v. drug addiction in five patients, and heterosexual and homosexual exposure in three patients each. The subsequent follow-up of lipomatosis ranged between 7 and 37 months, and was characterized by the appearance of further lesions in five patients (with one subject needing plastic surgery), and a substantially stable disease in the remaining 6 cases, while spontaneous regression of subcutaneous lesions never occurred. Lipomas and other benign tumors of fatty tissue have not been reported with increased frequency during HIV disease until recently, even after the introduction of HAART into clinical practice (Bornhord E et al., Br J Dermatol 2000; 143:1113-4). The apparent association of lipomatosis with other clinical and metabolic disturbances possibly related to HAART, should prompt accurate epidemiologic and etiopathogenetic investigations. In the single patient, malignant degeneration (although deemed extremely infrequent), should be carefully excluded.

PP 3.14.

Metabolic and Renal Profile before and after Tenofovir DF

Roca B, Gisbert C, Cabestany B, Perez AP, Ventura JM. Hospital General of Castellon, Spain

Background: Metabolic side effects are common with several anti-HIV drugs. Tenofovir disoproxil fumarate (TDF), a non-nucleotide reverse-transcriptase inhibitor, seems to be free of significant toxicity of that kind, although data are scant. Renal toxicity of TDF seems also uncommon, but more data on that is also needed. We assess patients' metabolic and renal profile before and after including TDF in their anti-HIV treatments.

Method: In a cohort of outpatients, we assess blood analysis four months before switching to TDF regimens (month -4), just before switching (month 0), four months afterwards (month +4), and eight months afterwards (month +8). All treatments are among those recommended by guidelines, and changes in drugs are made because of side effects or simplification of regimens. Patients with protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) switch in their treatments are excluded.

Results: A total of 23 patients are included. Mean $\pm$ SD of age is 38 $\pm$ 4 years; 15 (65 %) are male; 13 (56 %) are drug users; 13 (56 %) are hepatitis C virus co-infected; regimens include PI in 8 patients (35 %) and NNRTI in 15 patients (65 %). Table shows the results of blood analysis (mg/dl, mean $\pm$ SD).

Month	-4	0	+4	+8	P
Glucose	104 $\pm$ 18	108 $\pm$ 43	103 $\pm$ 15	96 $\pm$ 21	.015
Uric acid	5.1 $\pm$ 1.6	4.9 $\pm$ 1.8	5.2 $\pm$ 1.4	5.3 $\pm$ 1.9	.889
Total cholesterol	188 $\pm$ 43	197 $\pm$ 49	178 $\pm$ 40	173 $\pm$ 31	.002
HDL-cholesterol	46 $\pm$ 12	47 $\pm$ 15	41 $\pm$ 11	46 $\pm$ 12	.430
LDL-cholesterol	87 $\pm$ 35	84 $\pm$ 38	74 $\pm$ 34	75 $\pm$ 36	.254
Triglyceride	239 $\pm$ 198	267 $\pm$ 241	264 $\pm$ 302	211 $\pm$ 134	.553
BUN	14 $\pm$ 4	13 $\pm$ 4	14 $\pm$ 4	15 $\pm$ 4	.217
Creatinine	.9 $\pm$.1	.9 $\pm$.2	.9 $\pm$.2	.9 $\pm$.2	.772

Conclusion: TDF has a favorable short-term lipid and renal profile. A reduction in total cholesterol and glucose is observed in our cohort.

PP 3.15.**Cutaneous Drug-reactions associated to Nevirapine: study of risk factors in 101 HIV-positive patients**

Pitche P, Drobacheff-Thiebaut C, Gavignet B, Mercier M, Laurent R.

Department of Dermatology, CHU Saint-Jacques, Besançon, France

Background: Non nucleoside of reverse transcriptase inhibitors are recommended as part of an initial combined antiretroviral regimen or as an the intensification or rescue multidrug therapy in patients show poor reponse to Highly Active Antiretroviral Therapy (HAART). Most of studies showed a high prevalence of rash due to Nevirapine [1, 2]. But there is little knoweledge about the risk factors associated with rash induced by nevirapine [3, 4].

Objective: The aims of this study was to identify the risk factors associated with occurrence of rash during the treatment of HIV-positive patients with Nevirapine.

Methods: A retrospective study was conducted in dermatology department at Besançon's hospital between november 1998 to september 2001. Were included in this study all the patients infected by HIV1 wich received HAART including Nevirapine. Data collected were: age, sex, the mode of HIV transmission, CDC staging; CD4 and CD8 lymphocytes counts, plasma RNA level, serostatus of hepatitis B and C, Cytomegalovirus, antecedent of drug allergy, another associated treatment (others antiretroviral therapy, corticoïds, anti-histaminic drugs). The Chi-squared test or Fisher's test and Student's test were used in the univariate analysis; Cox proportional hazards model was used in the multivariate analysis.

Results: During the period of the study 101 HIV-positive patients (73 men and 27 women; mean age: 41, 4± 10, 3 year-old) were treated by HAART including Nevirapine. Fourteen of them developped cutaneous drug-reactions due to Nevirapine (13,86 %). We observed : 13 cases of maculopapular exanthema, 1 case of DRESS syndrome. In univariate analysis, the female sex ($p=0,002$), the plasma RNA level above 10.000 copies/mL ($p=0,05$), the heterosexual transmission ($p=0,002$), the patients pretreated by Abacavir ($p=0,05$) were the factors associated with rash. In the mulivariate analysis; only the female sex ($p < 0,0001$) and the plasma ARN level above 10.000 copies/mL ($p=0,0007$) were associated with the rash.

Discussion: The results of this study confirm the high frequence (9- 22 %) of rash associated to Nevirapine therapy [2]. The risk factors strongly associated of the occurrence of rash due to Nevirapine therapy are the female sex and the plasma RNA level above 10.000 copies /mL. In 4 to 9 % these cutaneous drug-reactions can be severe [5]. Several studies show not protective effect of antihistaminics and corticoïds to prevent the cutaneous adverses reactions associated to Nevirapine [6, 7]. The identification of the risk factors strongly associated with the Nevirapine-rash could help the physician to determine a new strategy for the use of Nevirapine in the HAART regimen. To prevent the Nevirapine-rash, the data of this study suggest that Nevirapine can not be initiated in the patients which has a plasma RNA level above 10.000 copies/mL, but after pretreatment with HAART including protease inhibitor, when the plasma RNA level is indetectable.

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PP 3.16.

HIV-HCV Coinfection. Hospital de Navarra (1995-2003)

Sola J, Gatesi C, Layana E, Castiello J, Reparaz J, Sola I. Servicio Enfermedades Infecciosas, Pamplona, Spain

Objetives: To study the factors involved in the evolution of AIDS patients and mortality in HIV patients with or without associated Hepatitis C (HVC) infection.

Materials and methods: Analytical cohort study of HIV infected patients followed-up from 1995 to December 2003 in the department of Infectious diseases. In all cases we detennined the age, date of HIV infection and HVC infection, date of AIDS presentation, date of death, CD4+count, CD8+count and viremia. The date of seroconversion VHC/HIV was estimated at the time of the first positive test. For statiscal analysis, we employed Cox's proportional hazards model. We established significance levels of 5%.

Results: The study included 660 patients of whom all the variables above mentioned were available. Of these patients, 228 (34,5%) presented HVC infection; 65 of these HVC patients developed AIDS (28,5%) whereas 136 (31.5%) who developed AIDS did not present coinfection. Relative risk of VHC/HIV was 0.88 (95% C1, 0.60-1.29). Mortality for HVC-HIV coinfection was 5.3%; while those with only HIV infection, 5.8%. The median of progression to AIDS in patients with CD4<200 was 7 years (25% after 6 months) while 80% of patients with CD4>500 were free of AIDS after 11 years. The increase in risk was 4.660 (95% CI:2.63-8.64). Age, p=0.009. Viremia, p=0.05.

Conclusions: Coinfection with HVC does not influence signifcantly the risk of developing AIDS. Risk in determined by the CD4+, CD8+ counts, age and viremia.

PP 3.17.**Study of HIV-infected patients attending an Intensive Care Unit (ICU).****Features and prognostic.** Comparative analysis between pre- and post HAART eras

Palacios R, Reina C, Santos J, de la Torre MV, Márquez M. Hosp. Virgen de la Victoria. Campus Teatinus, Málaga (Spain)

Objective: to analyse the clinical, epidemiological and outcome features of HIV-infected patients hospitalised in the Intensive Care Unit of our hospital and to compare the pre- and post-HAART characteristics.

Patients and Methods: demographic, epidemiological, clinical and analytical features of all HIV-infected patients hospitalised in our ICU between 1990 and 2003 are collected. Pre-HAART era: 90-96. Deaths in the ICU, in other Unit during the same income and later are analysed. Statistic program: SPSS.

Results: 66 patients. 87.9% men, mean age 39 years (21-73); HIV risk: IDU 56.4%, HMX 27%, HTX 16%. Mean CD4 cell count $231 \times 106/L$ (44-151). Respiratory diseases were the most frequent (11 PCP, 16 CAP, 1 NP). During the income (ICU-other Unit) 35 patients died (53.0%), 27 in ICU and 8 in other Unit. Survival rates of patients who did not die during that income were 60% at 1 year and 54% at 2 years. 56% of all cases were related to HIV infection, 43.2% (16/37) of them did not know their HIV serology, they were more immunosuppressed (CD4 51 vs $189 \times 106/L$; $p=0.022$) and PCP was more frequent than among previously diagnosed patients (81 vs 9%; $p<0.05$). Mortality was similar in both groups (68.7 vs 66.6%). Most patients who were hospitalised due to non-associated aids pathology were already diagnosed of HIV infection (85.7 vs 56.7%; $p=0.015$), they were less immunosuppressed (CD4 368 vs $138 \times 106/L$; $p=0.001$) and their mortality was lower (67.5 vs 32.1%; $p=0.006$). Among the 48 patients hospitalised in the HAART era, only 15 (31.2%) were on HAART. There were no differences between pre- and post-HAART eras.

Conclusions: a great number of the patients were diagnosed with HIV infection during their ICU hospitalisation, and most of them had PCP. Respiratory diseases are the most frequent cause of income in the ICU. Mortality is very high, mainly among aids associated cases. Patients who survive the ICU income have a survival rate greater than 50% at 2 years. There are no important differences between hospitalised patients in pre- and post-HAART eras. Less of a third of the patients who were attended during the HAART era were on antiretroviral therapy.

PP 3.18.**Fulminating Lactic Acidosis in a Woman with Disseminated Tuberculosis and Advanced HIV in the Absence of anti-retroviral Therapy**

Marshall BG, Rowen D, Addis B.

Southampton University Hospitals NHS Trust

Tremona Road, Southampton, SO16 6YD, Hampshire, UK

We would like to present a case of an African Woman who presented to our Hospital with extra pulmonary disseminated Tuberculosis predominantly involving her intra abdominal retroperitoneal lymph nodes. Her HIV status was uncovered at presentation, and had not commenced anti-retroviral therapy. She developed a profound lactic acidosis within a week of presentation and despite support in an Intensive Care Unit and institution of appropriate antimycobacterial therapy; the patient's condition progressed resulting in death.

The autopsy findings will be presented in detail as well as those mechanisms leading to the profound lactic acidosis.

PP 3.19.**Increasing AIDS "Presenters: a further concern of the Highly Active Antiretroviral Therapy (HAART) Era**

Manfredi R, Calza L, Chiodo F.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

Notwithstanding the introduction of highly active antiretroviral therapy (HAART) in the year 1996, full-blown AIDS still occurs, in the majority of cases in patients who missed or neglected their HIV serostatus. A prospective observational study of all AIDS cases notified by our centre in Bologna during the period 2001-2003 was carried out. All epidemiological and clinical correlates of newly diagnosed cases of AIDS were compared with those of all AIDS notifications performed in the pre-HAART decade (from year 1985 to 1995). When compared with the pre-HAART period, a significant drop of patients with newly diagnosed AIDS occurred (from a mean number of 58.3 ± 11.2 per year in the period 1986-1995, to 18.3 ± 7.9 per year during the last three years; $p < .001$). The analysis of demographic parameters disclosed an increase of mean patient's age ($p < .003$), and the female gender ($p < .03$). The investigation of epidemiological issues showed a proportional increase of sexual transmission (either heterosexual or homosexual), compared with i.v. drug use ($p < .001$), and an increased proportion of non-Italian citizens ($p < .04$). Among AIDS-defining disorders, both pneumocystosis and esophageal candidiasis ranked first in both time periods, followed by neurotoxoplasmosis, wasting syndrome, and AIDS-dementia complex. After the introduction of HAART as the standard of care of HIV disease in 1996, an early, significant drop of opportunistic infections involved several diseases linked to a very low ($< 50/\mu\text{L}$) CD4+ lymphocyte count, such as cryptosporidiasis, isosporiasis, and Cytomegalovirus, while a proportional increase of lymphomas, tuberculosis, and bacterial pneumonia remained of concern until now. The absolute number and the proportion of patients with multiple concurrent AIDS-defining diseases increased just in the HAART era (up to 7 in a single patient). The number of AIDS cases notified at the time of death also rose significantly ($p < .001$). On the other hand, the level of HIV-associated immunodeficiency at AIDS diagnosis did not prove different (42.3 ± 21.2 versus 48.1 ± 25.4 mean CD4+ cells/ μL). Surprisingly, a prior antiretroviral therapy proved more common among diagnoses made until 1995, as opposed to those identified during years 2001-2003 (64.3% versus 28.7%; $p < .001$), since the diagnosis of AIDS was increasingly made concurrently with HIV serodiagnosis, just in the most recent years. In conclusion, health care providers who face patients at risk for opportunism should continue to consider advanced, but still undiagnosed AIDS in their differential diagnosis, in order to ensure prompt recognition and adequate management of subjects with missed disease, or lost to follow-up, so that they did not have the possibility to take benefit from HAART.

PP 3.20.

The Potential of Volumetric Flow Cytometry to Follow up CD4 of HIV/AIDS Patients in Resource Poor Settings

Göhde W, Cassens U, Greve B.

Institute of Radiobiology, Institute of Transfusion Medicine, University Hospital, Münster, Germany

Despite billions of Euros and lots of national and international efforts HIV/AIDS remains a pandemic with a worse prognosis. Statistical calculations have shown that more than 5 million people are newly infected and more than 3 million HIV/AIDS patients died in 2003. Of course these values underline the dramatic situation but they can not deliver the hopeless reality happening in the developing world. With more than 36 million seropositive persons the whole African continent is particularly affected and actually the epidemic is spreading into the Asian continent and nobody can forecast the development. Projections for the next ten years suggest that the situation will become even more serious, with possibly 100 million infected individuals worldwide. Since more than 6 million people actually need treatment, the "3 by 5" program of the WHO can be recognized as a first approach to help them. Although generically produced antiretroviral (ARV) drugs are already available in sufficient quantities at a payable price, the necessary follow up of treatment success, either by CD4+ T-cell quantification or by viral load failed due to high reagent and equipment costs as well as high laboratory standard and experienced technicians associated with these tests. Based on our 35 year experiences in the development of adapted flow cytometry techniques we introduced a CD4+ T-cell counting device having the capacity to run more than 200 samples per day. The volume based flow technique enables the use of a simplified no-lyse no-wash sample preparation protocol that needs only 30 min for a batch of 20 samples from the beginning to the final result. The price for a single test is approximately 2 Euro. Data of 28 comparisons of this technique with conventional flow cytometry techniques from different African, European and Asian laboratories are presented.

PP 3.21. HIV-Associated Psychiatric Disorders

Farazi E.

Mashad University of Medicine, Iran

Patients with life-threatening illnesses face great psychological challenges and frequently experience emotional distress.

A major difficulty to the effective diagnosis of psychiatric problems in the medically ill is the understandable but incorrect notion that these problems are situationally appropriate response to medical disease. For example, many providers may believe that they, too, might be depressed were they facing the losses involved in having HIV disease.

When physical symptoms and suffering are controlled, it is easier to help patients think about their own psychological integrity, about finding meaning in their lives, and about their families. Physicians need to recognize the impact of psychiatric disorders such as depression, anxiety, and delirium at the end of life and develop skills in diagnosing and treating these syndromes. They help illuminate the potential opportunities presented when coping with life-threatening illness. Enhanced understanding of the common psychological concerns of patients with serious illness can improve not only the clinical care of the patient, but also the physician's sense of satisfaction and meaning in caring for the dying.

HIV infection is an example of a medical illness that is associated with psychiatric morbidity. As with any process that imposes high levels of stress on the body over a long period of time, the spectrum of consequences of HIV infection frequently includes psychiatric manifestations. Medically sicker patients are more apt to have psychiatric complications.

Thus it makes sense to diagnose these complications early, eliminate external causes, and treat this condition.

There is evidence that psychiatric disorders are common in patients with HIV and these patients have high rates of psychiatric morbidity.

but they may not receive optimal care because their psychiatric disorders are a barrier to medical care, communication with clinicians, and adherence to medical recommendations. It suggests an important role for general medical and psychiatric management of HIV-infected patients.

HIV patients can be considered medical patients who experience stressors with biological and psychosocial aspects. Psychiatric treatment requires a multimodal approach that combines psychopharmacological and psychosocial interventions.

Approximately 5000 persons are now infected with human immunodeficiency virus (HIV) in Iran. The abuse of drugs is known to increase the risk of HIV infection by direct intravenous transmission. It is the most common way of HIV transmission in Iran and after that is the sexual transmission. Substance abuse treatment can reduce intravenous drug use, and by decreasing the number of substance abusers with weakened immune systems, the ongoing transmission rates of HIV could be lowered.

The use of all substances, impairing judgement should be avoided because this leads to impulsive and risky behaviours, such as unsafe sex, and increases the risk of acquisition or transmission of HIV infection.

Detection of substance abuse disorders, especially those facilitating the transmission of infection or leading to noncompliance with medical treatment, is extremely important and can truly be lifesaving. Substance use or withdrawal can cause depression and psychomotor agitation so HIV patients with substance use should be screened carefully for depression, also depression itself predicts subsequent episodes of substance abuse, the treatment of depression in recovering HIV patients has an extremely important role in preventing relapse into abusing substances.

Psychiatric complications can also be due to social discrimination, and rejection by friends. Providing information to patients, families, friends and others would minimize alienation, social withdrawal, and rejection. A supportive network of family, loved ones, friends, and caregivers should be provided.

Family therapy is surely effective in mobilizing family support and in the resolution of serious family conflicts or stressors. This form of therapy can also help to reconcile issues in families who have rejected a person with AIDS.

Psychiatric complications in HIV can result from previous psychiatric conditions or the devastating psychosocial impact of having a non treatable,painful illness.Chronic pain like chronic headache due to HIV encephalitis , or chronic extremity pain due to peripheral neuropathy can cause depression and anxiety.

Optimization of pain reduction may improve the psychiatric disease.

The suicide rate in the HIV population is probably higher than that of the general population. Medical improvement in HIV patients leads to increased survival time and prolonged longevity for AIDS patients,and it also decresses psychiatric problems.

Religious and spiritual advicing, reading of holy books, prayers, and sharing in religious ceremonies have been shown to improve the coping strategies of patients sorrowing terminal illnesses, including HIV and AIDS. AIDS patients who participate in a religious conversion report a significant reduction in anxiety associated with the fear of death.

Educating AIDS patients about the possible emergence of psychiatric symptoms can cause early intervention either before or during the onset of diseases.Psychiatrists need to accurately diagnose and appropriately treat the psychiatric morbidity associated with HIV infection and sometimes Psychiatric referral of the HIV patient may be appropriate.Acutely suicidal HIV patients require emergency psychiatric hospitalization and clinically supervised observation during a crisis. The psychiatric evaluation and treatment of psychiatric morbidity improve the quality of life of AIDS patients.

PP 3.22.

Management of Hyperlactatemia in three HIV-positive Patients assuming ART

Moretti F, Quiros-Roldan E, Prestini K, Torti C, Casari S, Carosi G.

Department of Infectious and Tropical Diseases, University of Brescia, Brescia, Italy

Introduction

The antiretroviral therapy (ART) can induce mitochondrial dysfunction resulting in increased lactate formation which may be associated or not with acidosis. Generally, treatment of hyperlactatemia is based on stopping the ART, correcting the acidosis, if present, with bicarbonate, and supportive management.

Methods

Here, we report 3 cases of symptomatic severe hyperlactatemia (lactate serum level >5 mmol/L) in HIV-infected patients during treatment with ART in the Institute of Infectious and Tropical Diseases, Spedali Civili of Brescia.

Results

Three HIV-infected patients (pts) assuming ART were admitted in our clinic because of severe lactatemia. All three pts referred unspecific clinical symptoms including fatigue, nausea, vomiting and abdominal pain before coming to the hospital (pt. #1 from 60 days, pt. #2 from 7 days and pt. #3 from 1 day). All pts presented serum transaminase level and creatinine elevation.

The table shows epidemiological and biochemical characteristics of these patients.

Caractéristiques	Patient # 1	Patient # 2	Patient # 3
Age (years)	30	64	37
Sex	Female	Male	Male
Risk for HIV infection	Intravenous drug use	Homosexual	Intravenous drug use
Years with HIV infection (months)	108	9	108
Previous opportunistic infections	Cerebral toxoplasmosis	Disseminated CMV	Disseminated CMV and Cryptococcosis, Oesophageal candidiasis
Pathology associated	none	LNH	Cirrhosis
ARV duration (months)	AZT (8), 3TC (17), d4T (10), DDI (10), LPV/r (1), NFV (1), EFV (16)	DDI (9), d4T (9), EFV (9)	AZT (29), 3TC (31), DDC (25), DDI (5), d4T (17), SQV (6), IDV (17)
CD4 (cells/mm ³)	108	84	20
CD4 nadir (cells/mm ³)	45	61	9
Plasmatic viral load (cp/mL)	66000	< 50	9200
Serum PH	7.35	7.33	7.12
Serum Bicarbonate (mmol/L)	23.2	12.4	11
Serum base excess (mmol/L)	23.2	-13.8	-16.6
Serum lactate (mmol/L)	14.4	13.1	23.4
AST (U/L)	43	85	141
ALT (U/L)	35	115	78
Creatinine (mg/dL)	3.1	1.6	1.5
Lipase (U/L)	395	2747	804

In pts #1 and #2 additional agents were used for the therapeutical management of hyperlactatemia which included: dicloroacetate, isopropilammonio, thiamine, pyridoxine, riboflavin, cyanocobalamin (DCAi). The pts got normal levels of lactate in 3 and 19 days respectively. In pt #1, the evolution of the pancreatitis was favourable and it was resolved in 10 days.

The pt #3 was admitted to our hospital because intense abdominal pain and severe lactic acidosis (lactate level: 23.4 mmol/L and pH: 7.12). Pancreatitis was diagnosed and ART was immediately interrupted and initiated sodium bicarbonate continuous infusion. Therapy for pancreatitis was started but progressive worsening of clinical and laboratory conditions were observed (lactate: 26 mmol/L, pH 7.09, lipase 2876 U/L and creatinine 2.2 mg/dL). The patient had fatal outcome after 24 hours.

Discussion

In patients with severe lactate elevations (greater than 5 mmol/L) and acidosis, ART should be immediately stopped, even if symptoms are not referred by the patients. Here, we describe the use of dicloroacetate isopropilammonio, thiamine, pyridoxine, riboflavin, cyanocobalamin (DCAI) generally utilised for treatment of neuropathy as effective for treating symptomatic hyperlactatemia with acidosis in HIV-patients assuming ART.

PP 3.23.

Malabsorption and Septicaemia: Association in and Implications for Children in an Area of High HIV Prevalence

Chhagan MK, Kauchali S. University of KwaZulu-Natal, Nelson R Mandela School of Medicine, Durban, South Africa

Introduction: Gastrointestinal infections and malabsorption are highly prevalent in children with HIV infection. Carbohydrate malabsorption is reported to occur in 30 to 60% of HIV-infected children. Malabsorption may be a marker of risk of bacterial translocation and systemic sepsis.

The objective of this study was to describe the association between the presence of carbohydrate malabsorption and bacterial septicaemia in children with diarrhoea in a high HIV-prevalence area.

Methods: We studied clinical and microbiological data from a random sample of admissions during the period January to December 2001 to the paediatric diarrhoeal inpatient unit at a tertiary hospital in Durban, South Africa.

Results: Data from 319 patients were collected. Median admission age was 8.5 months (10th centile 2.5 months, and 90th centile 48 months). 61% of subjects were malnourished according to the Wellcome Classification. 66.7% had confirmed HIV infection and/or clearly defined clinical features that were highly suggestive of HIV infection. During hospitalisation, 31.4% of subjects had some evidence of carbohydrate malabsorption warranting modification of feeds. Of those that had blood cultures performed, 35/290 subjects (12%) had proven septicaemia. Of these, 71% were due to gram-negative organisms. Among these, *Klebsiella pneumoniae* (7/35) and *Escherichia coli* (6/35) predominated; followed by *Salmonella* species, *Acinetobacter* species and *Pseudomonas aeruginosa*. HIV status (16.8% of HIV infected vs. 3.1% of HIV uninfected, 95%CI of difference in proportions [3.2, 24.8%]), and presence of carbohydrate malabsorption (18.9% with malabsorption vs. 8.7% without malabsorption, 95%CI [1.2, 18.8%]) were strongly associated with septicaemia.

Discussion: The association between carbohydrate malabsorption and septicemia has not been widely described. We postulate that carbohydrate malabsorption may be a marker of impaired gut integrity and thus predisposition to bacterial translocation. The spectrum of organisms associated with septicaemic episodes in this study further supports the role of bacterial translocation in the pathogenesis of systemic sepsis. A high index of suspicion for septicaemia should be maintained in children with diarrhoea and malabsorption in regions where HIV infection and malnutrition are highly prevalent. These findings have implications for nutritional and antimicrobial management.

PP 3.24.

The Evolution of Surgical Practice in HIV/AIDS - A 16 years experience

Dua S, Wajed S, Winslet M.

University Dept of Surgery, Royal Free Hospital, Pond Street, London NW3

Aims

Surgical intervention has become a mandatory component in the management of patients infected with the Human immunodeficiency virus (HIV) or suffering from the clinical consequences of Acquired Immunodeficiency syndrome (AIDS). We investigate the evolution of this involvement at a tertiary referral centre for this condition over a sixteen-year period.

Methods

Detailed retrospective examination of the medical records of HIV positive patients treated at the Royal Free Hospital between 1986 and 2002 was undertaken. Clinical , pathological and operative details of those patients who underwent surgical intervention were recorded.

Results

Of the 2100 cases reviewed, 477 patients underwent a combined total of 772 surgical procedures. The majority were male gender (n=351, 73.6.%) the most common overall risk factor for acquiring the disease was sexual intercourse (88.88%). Of the 772 operations, 95 (12.3%) were performed as emergencies. A wide variety of disease-related procedures from virtually every surgical sub-speciality were carried out. Ano-rectal surgery represented the highest group with a total of 195 procedures (25.26%) being undertaken. The majority of patients (59%) had AIDS at the time of surgery, and 27.04% had a significant co-existing medical problem. Overall post-operative complication rate was 10.1%, with the risk being significantly greater in those undergoing emergency procedures, vascular surgery,intra-abdominal surgery, cardiothoracic surgery and those with a CD4 count below 200.

Conclusion

Medical treatment for patients with HIV/AIDS has developed dramatically over the last two decades. In parallel, this has resulted in a heavy, new and varied workload for all surgical specialities, which have also had to evolve in order to deal with the challenging spectrum of this disease.

PP 3.25.**ARVs Side Effects Leads To Poor Compliance Hence Resistance**

Byaruhanga BR, Mugenyi MP, Kityo KC, Otim OT, Mwebesa MD.

Joint Clinical Research Center, Kampala, Uganda

Purpose:

To find out whether clients who are given free ARVs and monitored freely get improved compliance.

Methods:

The study was carried out at the Joint Clinical research Centre, Kampala. 50 clients were enrolled in to the study and were given free ARVs for 2 years. 20 were male while 30 were female. They were given these free ARVs which included saquinavir, ritonavir and combivir.

Results:

Out of 50, 12% withdrew their consent because of serious side effects. these side effects Include nausea. Vomiting and diaohreea. Majority of the clients who withdrew were male.

Conclusion:

Free ARVs does not mean good adherence despite the fact ARVs were given free of charge to poor HIV positive clients, many of them withdrew their consent therefore a need to improve on treatment.

PP 4.1.
TMC114/RTV Activity in PI-experienced Patients: correlations of baseline genotype, phenotype, PK and IQ with antiviral activity at day 14 :

Peeters M, Van Baelen B, De Meyer S, de Bethune MP, Muller H, Hoetelmans R, Lefebvre E.
Tibotec Inc., Yardley, USA; Tibotec, Mechelen, Belgium

Background: TMC114 is a potent, next generation HIV protease inhibitor (PI) with in vitro antiviral activity against both wild-type and PI-resistant HIV-1.
Design: In TMC114-C207, an open, randomized Phase IIa study, patients on a virologically- failing regimen received TMC114/RTV as a substitute for all PIs or continued their current regimen (control group). Multi-PI, 2- or 3-class experienced patients received TMC114/RTV at doses of 300/100 mg bid (N=13), 600/100 mg bid (N=12) or 900/100 mg qd (N=13) for 14 days. Change in viral load was determined over 14 days; baseline genotypic and phenotypic testing were performed. This analysis investigated the antiviral response in specific subgroups and the correlation between antiviral activity and baseline phenotype, genotype, PK parameters and IQ.
Results: 38 patients were randomized to the treatment arms. The median baseline viral load was 4.3 log10 copies/ml and the median CD4+ cell count 305 cells/mm3. Median changes in viral load were -1.2, -1.3, and -1.5 in the 300/100 bid, 900/100 qd and 600/100 bid group, respectively. There was no statistical difference in antiviral activity between the 3 arms. All TMC114/RTV groups were statistically superior to the control group (p<0.001).

The table below presents antiviral activity observed in specific subgroups at baseline:

Subgroup	Median change in log viral load, day 14 (min ; max)
All Treated Patients (N=35)	-1.4 (-0.5 ; -2.5)
TMC114/RTV patients with >1 primary PI mutation (N=28)	-1.4 (-0.5 ; -2.5)
TMC114/RTV patients with phenotypic resistance to all approved PIs (N=19)	-1.5 (-0.5 ; -2.5)
TMC114/RTV patients with phenotypic resistance (FR>10) to lopinavir (N=28)	-1.5 (-0.5 ; -2.5)
TMC114/RTV patients with viral load >20000 copies/ml (N=14)	-1.5 (-0.9 ; -2.5)

In these subgroups, no differences in antiviral response were observed. Univariate analysis showed that genotypic, phenotypic, PK and IQ parameters were not predictive for change in viral load at day 14.

Conclusions: In this highly treatment-experienced population, all TMC114/RTV groups demonstrated a robust viral load response. Baseline susceptibility to TMC114, as well as PK parameters and IQs for TMC114, were not predictive for the change in viral load at day 14, indicating that the selected TMC114/RTV doses provided exposures sufficiently high to overcome broad resistance to PIs.

PP 4.2.**Impact of the Adverse Effects of HAART in Various Clinical Situations on the 3/5 Initiative of WHO-resource Limited Country Setting: a pilot study**

Ketha P. State Nodal Officer for the Control of AIDS, Project Implementation Plan, Phase II, National AIDS Control Organisation, Andhra Pradesh ,INDIA

AIM :To strengthen the 3/5 Initiative of WHO in the Resource-limited country settings through the effective management of the adverse effects of Anti-Retroviral therapy and promoting good compliance.

BACKGROUND: WHO has set a goal of 3/5, hoping that wider access to ART will stimulate prevention and there will be positive impacts on social and economical development as people living with HIV live longer and more productive lives. At least three million people should be given access to the life-sustaining ART by the end of next year. A study was done in sixty patients on HAART in North Coastal Andhra Pradesh, for a period of two years, to set a model for the naïve patients in resource-limited country setting, for the means of effective management of the adverse effects of Anti-retroviral drugs used in the combination of Lamivudine, Zidovudine and Nevirapine in various clinical settings.

MATERIALS AND METHODS:Initially screened with rapid test (tridot) followed by Western blot testing; CD4 counts (flow cytometry) evaluation and Viral Load estimations (RT PCR), HAART started appropriately, and monitored. Relevant investigations were repeated periodically. Few cases demanded hospital admission for various compelling issues like, for monitoring the general adverse effects in patients who were with very low CD4 and very high Viral loads, for improving compliance in cases of GI intolerance and Hbs Ag positive patients, for recognizing drug interactions with ATT, Anti-fungal, Anti-convulsants, and in seriously ill patients in cases of co-infections with TB, malaria, meningitis. Adverse effects were managed well.

RESULTS: The GI intolerance (30%) is common in both sexes. Hyperlipidemia (15%) is found to be more common in males. Skin lesions (10%) are found mainly in the females (Nevirapine). Hyperglycemia (6%) is equally uncommon in both sexes. Liver dysfunction is not encountered even with concomitant ATT. The adverse events are more common in patients with low CD4 counts and high viral loads. Two cases of meningitis developed repeated convulsions due to low levels of phenytoin and two cases of leucopenia due to Zidovudine were encountered.

CONCLUSIONS: The Antiretroviral therapy only when coupled with the facilities for exhaustive health education, counseling and the proper infrastructure for strategic and planned approach for the effective management of adverse effects would make the 3/5 initiative of WHO successful.

PP 4.3.

Care and Treatment Issues of PLWHAs in Resource Poor Conditions

Agrawal R & Ghosh P.

Bhoruka Public Welfare Trust, Kolkata, India

This paper reviews and analyses the importance of home and community-based care for PLWHAs in the resource constraint settings of Eastern India. The strategy adopted for 194 PLWHAs (among whom 31 are children below 10 years, and the male: female ratio is 135:59) has been successful in providing continued social, medical, psychological support and nursing-care under severe resource constraints.

The family-based care is provided through counseling and training of all the members on different aspects of prevention, treatment, nursing-care, nutrition and hygienic practices. The community support is provided through the formation of community extension units comprising of PLWHAs, counselors, health care providers, local influential people, NGOs and CBOs. It was revealed that this approach has the following advantages: a) Basic and simple care could be provided at home. b) Psychological support, which is most essential component of both physical and mental well being of the PLWHAs is provided by counseling of the individual, through the family support. c) Home-based care is cost effective than hospital care. d) Encourages the family to take the roles and responsibilities of the PLWHAs. e) Lessens the burden for health personnel in caring for the patients. The community-based care not only provides psychological support for the PLWHAs and their families but also helps to fight the stigma, discrimination and ostracization through the creation of patient friendly environment. The family responsibility helps in early diagnosis of opportunistic infections, inculcates positive health seeking behaviour and ensures better patient compliance. Maintenance of hygienic practices helps in prevention of opportunistic infections and proper nutrition helps in delayed break down of immune system. Through this approach 138 patients are keeping quite well even after three years of diagnosis without anti-retroviral therapy while just 25 of them are on ARV drugs where it is clinically and immunologically indicated. Of the rest 31 individuals, most of whom were diagnosed late, are in advanced stage of the disease and are hardly responding to any treatment. But even they are being well cared for at home.

PP 4.4.

Scaling up Antiretroviral Therapy in Jamaican Children

Evans-Gilbert T, Pierre R, Steele -Duncan J, Rodriguez B, Whorms S, Figueroa, PJ, Christie CDC. Bustamante Hospital for Children Kingston, Jamaica

Background: We describe a cohort of HIV infected Jamaican children receiving antiretroviral therapy (ART) and report the outcomes of this intervention.

Methodology: An observational multicentre prospective study was conducted . Children commenced ART using clinical, immunological and compliance indicators .Outcome measures included anthropometry, hospital admissions and length of stay.

Results: There were 37 (18%) of 204 HIV exposed and infected children receiving ART during 2001-2003. The mean age at commencement was 7.35 ± 4.63 years (95%CI 5.81,8.89; $p < 0.0001$) with 20 (54.1%) males. AIDS orphans represented 48% of cases. Care was home based for 68 % of cases. The University of the West Indies managed 27(73%) cases and the Bustamante Hospital for children managed 10 (27%) .The distribution by CDC clinical classes were C, 22(59.5%), B(21.6%),A , 6(16.2%) and N, 1(2.7%). Among 14 (36%) children with CD4 counts 8 (57%) were CDC immune class 2 and 6 (43%) were class 3. The mean difference in admissions was - 1.5 ± 2.6 admissions (95 % CI -2.3, -0.6; $p < 0.001$).The mean difference in length of stay was -12.9 ± 21 day (95 % CI -19.9, -0.5; $p < 0.001$). Antiretroviral therapy resulted in a mean weight gain of $2.8 \text{ kg} \pm 4.9 \text{ kg}$ (95% CI 1.0, 4.5; $p < 0.003$) and a mean height gain of $1.7 \text{ cm} \pm 2.6 \text{ cm}$ (95% CI 0.6, 2.8; $p < 0.003$).Six children failed initial therapy , due mainly to compliance issues .Challenges included diagnosis, laboratory monitoring for immune reconstitution and resistant strains and financial sustainability.

Conclusions Antiretroviral therapy is being initiated in older children funded mainly by families resulting in clinical improvement. Compliance is key for sustained results. Affordable markers of immune reconstitution and viral resistance are needed.

PP 4.5.

About Early Atazanavir Availability in France

Vivona V, Vincentelli J, Drogoul MP, Marimoutou C, Poizot Martin I, Penot Ragon C, Gastaut JA. Pharmacie Hôpital, CISH-SUD Unité d'Hématologie-VIH Hôpital Sainte Marguerite, Marseille, France

Atazanavir (ATV) is a new once a day protease inhibitor (PI) recently approved in France. From January 2002 to March 2004, AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) allowed ATV prescription through "Autorisation Temporaire d'Utilisation" (ATU) for HIV-1 infected, antiretroviral (ARV) experienced patients with severe lipid profiles, uncontrolled with hypolipidemic treatment, associated or not with cardiovascular risk. As ATU was nominative, all cases were studied one by one and no specific criteria was given for requests. About 300 patients (out of 600 requests) benefited ATV ATU countrywide. They were 10 out of 20 in our hospital unit. Accepted (A) and refused (R) patients were compared to understand which criteria of inclusions were relevant to obtain ATV ATU. A and R were comparable for median age (43 years), sex (90% male), median delay of HIV+ (14 years), mean ARV molecules used (13) mean PI prescribed (5) and median HIV plasma RNA (5 log/ml). Mean ATV possible resistance mutations were 8.88 (n=9) and 7.6 (n=7) for A and R respectively. R were twice more classified C3 than A. Median [QD] CD4 cell count was 50% less for R than A (102 [4-518], 204 [4-510] cells/mm³). Total cholesterol distribution was: Mean (range) 4.52 (2.31-6.5) for A and 4.92 mmol/l (2.51-8.03) for R. Mean triglyceride A: 4.81 (1.42-8.18), R: 3.70 (2.19-5.08) mmol/l. Six patients were under hypolipidemic treatment (2A and 4R), and one A had experienced heart disease. AFSSAPS gave four reasons of non-agreement for R patients: possible ARV or hypolipidemic alternative therapy (3/10), minor or absent lipid disorders (3/10), no proof of efficacy in lipodistrophy (1/10), highly pretreated patient with high risk of PI cross-resistance (6/10). Even if reasons evolved during ATU period in regard of updated data, we identified among our R cases late stage of HIV disease, lower immunity and a trend in favor of lower triglyceride level as non inclusion-criteria. For A patients, mean treatment duration was 5,3 (0,5-13) months. Four of them still continue after ATV commercialization approval (2 treated for more than 12 month). Low effective does not allow any interpretation on ATV efficacy. Four patients stopped for lack of response and two for adverse events.

By evidence, ATU status is necessary for HIV infected patients but it seems difficult for both AFS-SAPS and prescriber to study each case relevance since no precise criteria are previously defined for nominative ATU request.

PP 4.6.**Prise en Charge Communautaire des PVVIH Soins de Santé de Base à Domicile par les Jeunes Volontaires en Lutte contre le SIDA (AJVLS) : visite à domicile dans Lomé-Commune (TOGO)**

Association des Jeunes Volontaires en Lutte contre le SIDA (AJVLS), Lomé, Togo

Malgré les récents progrès thérapeutiques, le VIH/SIDA demeure toujours une maladie sans traitement curatif. La prévention des nouvelles infections à VIH et la prise en charge des personnes vivant avec le VIH restent donc les seuls moyens d'endiguer l'épidémie et d'atténuer les ravages qu'elle fait au sein de la communauté. C'est dans ce cadre que l'Association des Jeunes Volontaires en Lutte contre le SIDA (AJVLS) a élaboré un plan d'action pour la prise en charge des personnes vivant avec le VIH au sein des confessions religieuses en collaboration avec le Programme des Nations Unies pour le Développement (PNUD) et une enquête de recherche opérationnelle a été menée et les résultats ont prouvé que ce programme de prise en charge s'avère nécessaire pour venir en aide aux milliers de personnes vivant avec le VIH regroupée au sein de confessions religieuses. De ce fait, l'Association des Jeunes Volontaires en Lutte contre le SIDA (AJVLS) a organisé des services conseils et soutien psychologique aux PVVIH ainsi que de traitement, Visites à domicile aux PVVIH et aux membres de leurs familles sont organisés par semaine, promotion et soutien aux activités génératrices de revenus démarrés par les PVVIH, élaboration d'un guide sur la prise en charge des personnes vivant avec le VIH/SIDA (PVVIH) et de leur famille destiné aux conseillers visiteurs à domicile des PVVIH et la confection des KITS de soins des PVVIH. La méthodologie consiste à former les leaders des confessions religieuses sur les IST/SIDA et la prise en charge des PVVIH et les Pairs Conseillers ou Visiteurs de domiciles, mettre sur pieds des cellules sida composés des leaders et les Pairs conseillers. Les visiteurs de domicile recensent les malades, veuves avec orphelins démunies atteint du sida ayant des orphelins à charge et leur accorder une aide financière pour la création de petit commerce en vue de promouvoir leur autosuffisance. Les sensibilisations se font à travers les prêches par les leaders.

Activités réalisées et résultats obtenus / Activities led and results achieved :

- Formation des responsables et leaders religieux, - Formation des fidèles religieux pairs conseillers, Formation de veuves vivant avec le VIH sur les activités génératrices de revenus, - Financement de veuves pour des activités génératrices de revenus, - Comité de suivi avec les confessions religieuses impliquées, - Conseils pré et post test dépistage au VIH et consultations médicales, - Les visites à domicile, aux PVVIH et distribution de Kit de soins de base, - Les séances d'éducation des pairs conseillers, des pairs éducateurs et des leaders religieux, - Guide de prise en charge pour les conseillers de visites à domicile.

Leçons apprises et étapes futures / Lessons learnt and future stages :

- La discrimination des PVVIH dans les localités est due en grande partie à l'ignorance de la maladie du SIDA, aux tabous et aussi à certaines valeurs culturelles néfastes, L'implication des communautés et les structures sanitaires est un élément facilitant dans la gestion du programme, Les volontaires impliqués dans les activités de prise en charge doivent être motivés suivant leur dynamisme, Sur le terrain il faut qu'il y a une coordination des activités de prise en charge entre les ONG de prise en charge et l'Association des Jeunes Volontaires en Lutte contre le SIDA (AJVLS).

PP 4.7.
Close Collaboration between Physician and Virologist for a Stage CDC-3 AIDS Patient : importance of genotype assessment for the choice of efficient antiretroviral therapy

Duliuost A, Naudin CA, Cottreau D, Jauneau M.
Centre Médical de Bligny, Briis/forges, France

Introduction

We describe a stage CDC-3 HIV infected patient who did not respond to numerous lines of antiretroviral drugs. Using a therapeutic window combined with genotype assessment led to an improvement of both clinical condition and biological parameters.

Description of the case

After seven lines of antiretroviral treatment, between 08/1996 and 08/1999, the patient was in poor medical condition with many drug-related adverse events. Viral and immunological assessments were the followings: CD4, 27/mm3; viral load, 4.7 log10. Moreover, several mutations were evidenced at resistance sites: I69SS + A98G + V108I + Y181C + G190S + L210W + T215Y ; (PR gene was not amplified).

After a 10-month wash-out period, the patient was hospitalized for a CMV retinitis. Genotype determination evidenced a major wild-type HIV strain. Under a quadritherapy (CBV, ABC, LPVr) good clinical and virological responses were observed after 1 month. However immunological parameters were not improved. After 3 months, the virus again escaped (viral load, 5.6 log10; CD4, 14/mm3) and genotype was I69SS + V32I + M46I + A71V + V77I and V82A. Treatment was then switched to LPVr, APV, EFV and TDF, but without any improvement.

A new therapeutic window was opened for 3 months. The I69SS insert was still present and new resistant sites mutations appeared leading to a class resistance to INNRT and additionnal resistances to APV and IDV (CD4 count: 3/mm3; viral load: 5.3 log10). A treatment including 3 boosted PI and 2 INNRT, according to the mutation's profile (LPV, SQV, IDV, 3TC, TDF) was administered in September 2002.

The patient gained weight and the viral load is now undetectable since several months with a CD4 cell number at 400/mm3:

date	Log10 viral load		CD4/mm3	CD4/CD8
10/2002	3.0	7	0.02	
01/2003	< 1.3	59	0.1	
03/2003	< 1.3	115	0.15	
10/2003	< 1.3	329	0.28	
02/2004	< 1.3	400	0.25	

Conclusion

This observation over a period of 8 years strongly suggests that HIV patients could benefit of a close cooperation between virologists and clinicians for the choice of efficient antiretroviral therapy according to viral genotype and patient drug tolerance

PP 4.8.**High Prevalence of Nephrolithiasis in HIV- infected Patients Co-infected with Hepatitis C Virus Treated with Indinavir+Ritonavir**G. Dragovic¹, Dj. Jevtovic²

1 - Institute of Clinical Pharmacology; Pharmacology and Toxicology, School of Medicine, University of Belgrade, Belgrade, Serbia and Montenegro; 2 - Institute of Infective and Tropical Disease - HIV/AIDS Unit - School of Medicine, University of Belgrade, Belgrade, Serbia and Montenegro

Background: Using Ritonavir (RTV) as a pharmacoenhancer of Indinavir (IDN), it results in increased exposure to the IDN, higher C_{min} levels, prolonged elimination half-lives, as same as long-term toxicities. The objective of this study was to examine if IDV (400 mg BID) boosted by RTV (100 mg BID) in combination with nucleoside reverse transcriptase inhibitors (NRTIs) was associated with a higher risk of nephrolithiasis in HIV-infected patients co-infected with hepatitis C virus (HCV). **Methods:** We performed prospective, open-label, follow-up study and continuously monitored drug naïve HIV-infected patients for incidence cases of nephrolithiasis. Data were obtained from patients continuously monitored for incident cases of nephrolithiasis at the HIV/AIDS Unit, a University teaching hospital, Belgrade, Serbia and Montenegro. There were two groups of patients: HIV-patients who were not infected with HCV (I-group: HIV+HCV-) and HIV-patients who were co-infected with HCV (II-group: HIV+HCV+). The same treatment was given to both groups of patients. The prevalence of nephrolithiasis between groups of patients was compared using the chi-square test. Univariate and stepwise Multivariate logistic regression were used in order to estimate the probability of developing nephrolithiasis.

Results: In a cohort of 69 HIV-infected patients, 32 patients were in the I-group and 37 patients were in the II-group. Thirteen cases of nephrolithiasis were recorded during the time period from February 1999 to February 2003. The prevalence of nephrolithiasis was 12.5% (4 patients) in the I-group vs. 24.3% (9 patients) in the II-group ($p < 0.005$; $df = 1$). Multivariate logistic regression analysis shown that the relative risk (RR) of developing nephrolithiasis is 2.1 folder higher ($RR = 2.1$; 95% CI 1.05-5.69) in the I-group and 5.8 folder greater in the II-group ($RR = 5.8$; 95% CI 2.16-9.82). **Conclusions:** In our study, we demonstrated that boosting IDV with RTV increased the risk of developing nephrolithiasis, as a toxic effect of IDN, by 5.8-fold in HIV-patients co-infected with HCV. We support the need for therapeutic drug monitoring in patients using IDV with or without RTV in HIV+HCV- and/or HIV+HCV+ in order to monitor the number of patients who discontinued IDV due to toxicity.

PP 4.9.

The Phenomenon of HIV-infected Patients taking only Isolated Dual Nucleoside Analogue Antiretroviral Therapy, Eight Years after HAART Introduction. Practical issues and concerns

Manfredi R, Calza L, Chiodo F.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

No controlled figures exist about the evolution and outcome of patients on isolated dual anti-HIV therapy, although this phenomenon still exists in daily practice. At our outpatient HIV centre, patients who rely on a dual nucleoside analogue treatment only are slightly <20% of the around 900 treated ones. A 55-year-old patient with diabetes mellitus and familial hyperlipidemia started antiretroviral therapy in the year 1996 with optimal adherence: zidovudine-didanosine were administered for six months, followed by didanosine-stavudine for 12 months, while lamivudine-stavudine are continued since 51 months. Plasma HIV viremia ranged from undetectable values to 3,700 HIV-RNA copies/mL throughout the entire follow-up period, so that a genotypic resistance testing was not feasible. Absolute CD4+ lymphocyte count varied between 384 and 760 cells/ μ L. A 39-year-old patient co-treated with antidepressant drugs, started his antiretroviral treatment 6.5 years ago with continued good compliance levels: zidovudine-didanosine were administered for 14 months, followed by a 17-month stavudine-lamivudine combination. A protease inhibitor-based regimen was introduced since mid-1999, but later during the follow-up four-drug combinations became necessary due to repeated virological rebounds and associated therapeutic failure. Repeated genotypization showed a complete resistance to all tested anti-HIV compounds. In this subject, a favorable clinical and immunological situation led to a late HAART introduction. The use of isolated dual nucleoside analogues, carried out for 31 months in absence of stringent indications for a triple regimen, can be therefore discussed: such a suboptimal approach was perhaps responsible for an extensive multi-drug resistance, which contrasts with a substantially stable evolution of HIV disease. Multiple genotypic resistances now make very difficult to select an effective regimen for our patient. Both the presented patient courses point out a stable HIV disease evolution under long-term isolated dual nucleoside analogue therapy, continued also during the HAART era. On the other hand, extensive resistance seems to stem from a breaking of an unstable balance triggered by the introduction of a low-potency protease inhibitor (saquinavir hard gel in the second patient), recommended during years when also a viremia below 104 HIV-RNA copies/mL suggested this choice. In the first case report, a patient at potential risk of adverse events related to the introduction of every drug other than nucleoside analogues, continues to have a long-term satisfactory course. Since controlled data are not available, the large majority of posed questions will remain unanswered, and probably the long-term balance among HIV infection itself, immunological and genetic background, turnover of peripheral CD4+ lymphocytes, and the even suboptimal effect of two nucleoside analogues, seem to be borne by a very reduced risk of modification through time, and probably does not require short-term drug interventions. Antiretroviral treatment intensification, despite its greater intrinsic potency, may be responsible for the induction of a negative evolution, among increased adverse events, reduced patient's adherence rate, and viral resistance spread.

PP 4.10.**Impact of the HCV Co-infection in Naïve HIV-1 Infected Patients Treated with HAART**

Silva S, Ferreira A, Tavares M, Piñeiro C, Xerinda S, Serrão R, Diaz-Brito V, Marques R, Mota Miranda A. Infectious Diseases Department, Hospital S. Joao & School of Medicine, Porto, Portugal

Background: Viral hepatitis potentiates the hepatotoxicity of the antiretroviral drugs. We aim to evaluate the impact of HCV co-infection on the frequency of liver damage and on the immunological and virological response to HAART. **Methods:** retrospective study of all naïve HIV-1 infected patients (pts) who had an HAART regimen instituted after Jan. 2002 and completed >3 months of therapy. The study collected demographic and safety data, viral load (VL), CD4 cell count (CD4) and treatment history. Pts were grouped according to their HCV infection status. HBsAg positive pts were excluded. **Results:** The clinical files of 163 pts were reviewed. 73 (45%) pts were HCV co-infected (group 1): mean age 35 ± 6 years, 88% male. 90 (55%) pts without HCV (group 2): mean age 43 ± 13 years, 67% male ($p<0.01$). At baseline: mean VL (cps/mL) and CD4 (cells/cmm) were respectively $323\ 920$ (108000-1000000) and 145 (3-887) in group 1 and $432\ 811$ (103000-1000000) and 142 (7-742) in group 2 (no statistically significant difference). The ARV regimen contained 2 NRTIs plus: PI (45% group 1, 42% group 2); NNRTI (51% group 1, 56% group 2). 3 NRTIs in 4% (group 1) and 2% (group 2). Mean time under therapy was 13.5 ± 6 months in group 1 and 12.6 ± 6 in group 2. The mean increase in CD4 was 157 ± 143 /cmm (group 1) and 210 ± 176 /cmm (group 2) ($p=0.05$). The mean decrease in VL (cps/mL) was 36117 ± 43923 (group 1) and 48238 ± 33414 (group 2) ($p=0.028$). At any time during therapy a grade 3-4 elevation in AST/ALT was registered in 4% pts (group 1) and in 0% pts (group 2) ($p<0.05$); grade 3-4 elevation of gama-GT in 12% pts (group 1) and in 1% pts (group 2) ($p<0.05$). The regimen was modified in 28% (group 1) and 20% (group 2) and was discontinued in 8% (group 1) and 6% (group 2) - due to hepatic toxicity in 12.5% pts of group 1; none in group 2 discontinued therapy due to liver toxicity. **Conclusion:** HCV co-infection in these naïve HIV infected pts was shown to complicate their therapeutic management and to impair the CD4 recovery and the virological response to the antiretroviral therapy.

PP 4.11.

Nelfinavir in HCV - HIV coinfecting patients: 24 Months' follow up

Poizot-Martin I, Marimoutou C, Drogoul-Vey MP, Vion-Dury F, Frixon-Marin V, Benhaim S, Poggi P, Gastaut JA.

CISIH-SUD- Hematology- HIV Unit, Clinical Research Department Sainte-Marguerite Hospital, CHU of Marseilles, France

Background: The risk of antiretroviral-induced liver toxicity is increased in patients with chronic liver disease caused by hepatitis C or B. Both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors have been incriminated. Long term safety of nelfinavir in HCV - HIV coinfecting patients (pts) in routine practice is not yet established.

Objective : To evaluate safety and efficacy of nelfinavir (NLF)- antiretroviral combined regimen in 82 HCV - HIV coinfecting patients.

Methods: Retrospective analysis of therapeutic data of the 341 HCV - HIV Cohort of CISIH-Sud clinical unit. We selected the patients treated with NLF at inclusion in the cohort (baseline) with available biological results during the follow-up. Data were analysed in under therapy procedure using Chi2, or Kruskal-Wallis tests.

Results: At baseline, the median age was 36.4 years (Interquartile Range (IR):34-39.8), 36.6% were females. The median delay of NLF exposure was 4.1 months (IR 1.7-8.5) and patients were in median under their second line of PI (IR:1-3). NLF was combined to nucleoside reverse transcriptase inhibitors (NRTI) in 58 patients (tritherapy: 56) and to NNRTIs in 24 patients (efavirenz: 8; nevirapine: 14; tritherapy: 16; quadritherapy: 7). Median follow up was 23 months (IR: 14 -37) and 82% remained with the same antiretroviral combination during the follow up. At baseline, median CD4 cell count was 337 /mm3 (IR: 216- 480) and 39.7% had an undetectable HIV-RNA level (median VL: 269 copies/ ml (IR: 200- 4681). Qualitative HCV -RNA was positive in 91 % of patients and 56.2% of them were infected with genotype1. Among the 57 patients with liver biopsy, Metavir score was over F2 in 34% and 19.6% of them had cirrhosis. Median Alanine and Aspartate Amino-transferase (ALAT, ASAT), Gamma Glutamyl Transferase (GGT) and Phosphatases alcalines (PAL) were respectively 46 UI (IR: 36-76), 55 UI (IR 32-97), 97 (IR: 50-194) and 88 UI (IR: 72-104) with 76% of patients with grade 0 or 1 transaminases levels. No significant difference was observed at 24 months (n = 37) with median ALAT, ASAT, GGT and PAL being respectively 48 UI (IR: 34-66), 50 UI (IR 26-80), 111 UI (IR: 35-212) and 82 UI (IR: 73-97) and 86% of patients being grade 0 or 1. Patients treated by NLF plus NNRTI had significantly higher GGT and PAL level since cohort- baseline with no significant increase during the follow up. As well no significant difference was observed on cholesterol, triglycerides and glycemia median levels. Therapeutic response was improved with 55.6% of undetectable VL (p=0.01) and median CD4 cell count of 392/mm3 (IR: 280-558) (p= 0.05).

Conclusion: Long term Nelfinavir (NLF)- antiretroviral combined regimen is effective and well tolerated in HCV - HIV coinfecting patients. In particular, we did not observed any pejorative liver impact. Furthermore, lipid and glucid profile remained stable during the follow up.

Supported by Roche Industry.

PP 4.12.

Predictive Factors for Saquinavir-ritonavir combination (SQV/r) Efficacy in Real Life

Tissot-Dupont H, Mars-Kallee ME, Montestruc F, Tomei C, Martin S, Lecomte V, Gallais H.
La Conception Hospital, Marseille, France ; Roche Laboratories, Neuilly-sur-Seine, France

Objective: To determine factors predicting efficacy of SQV/r in real life

Patients and Method: Between 01-1996 and 11-2003, 254 patients have initiated a SQV/r combination in this cohort. At each visit during therapy, observance, viro-immunologic efficacy and clinical and biological safety were noted prospectively.

Results: Median HIV therapy was 4 years (min 0- max10 years), 85% had received ≥ 3 ARV sequences. At enrolment median CD4 count was 262/mm³ (3-886), and median viral load was 4 log (1,4 - 6,3). Prognostic factors for virologic response (VL<50 cp/ml) were analysed with a logistic regression

*Univariate, **multivariate °not significant °no applicable	M6		M12		M18		M24	
Nb patients in study	208		179		132		112	
OT VL< 50 cp/ml (nb/%)	87/42%		82/46%		71/54%		61/55%	
Analyse p/(Odd Ratio)	Uni*	Multi*	Uni*	Multi*	Uni*	Multi*	Uni*	Multi*
Previous Nb of ARV strategies used > 3	0.03 (0,50)	NS°	0.003 (0,35)	0.0034 (0,30)	NS°	NS°	0.007 (0,29)	NS°
Baseline VL > 10 000Cp/ml	<0.001 (0,24)	<0.001 (0,21)	0.01 (0,46)	<0.001 (0,21)	<0.001 (0,46)	<0.001 (0,12)	NS°	0.02 (0,35)
Baseline CD4 < 200/mm ³	NS°	NS°	NS°	NS°	NS°	NS°	NS°	NS°
Δ VL at M3 > -1log	<0.001 (2,77)	NA°°	0.003 (2,55)	NA°°	NS°		NS°	NS°
Δ VL at M6 > -1log	NA°°		<0.001 (4,24)	<0.0001 (6,76)	0.02 (2,42)	<0.001 (5,55)	0.03 (2,33)	0.01 (3,41)

Discussion and conclusions : It is usual to say: "it is better initiating a treatment when VL is low and CD4 count is high". This study confirms the first statement but not the second one. In our study carried out in heavily pre-treated patients in real life, an another important predictive factor is the decrease in VL>1log at M6. This factor is predictive for virologic response at M12, M18 and M24, whereas the decrease in VL>1log at M3 is not, suggesting that at least 6 months therapy with SQV/r is required before considering a switch for virologic failure in heavily pre-treated patient.

PP 4.13.

Saquinavir-ritonavir Baby Dose Combination (SQV/r) : Same efficacy and better tolerance in real life than Saquinavir-Ritonavir high dose (SQV/R)

Tissot-Dupont H, Mars-Kallee ME, Montestruc F, Tomei C, Martin S, Lecomte V, Gallais H.
La Conception Hospital, Marseille, France ; Roche Laboratories, Neuilly-sur-Seine, France

Objective: To compare SQV/r efficacy and tolerance to SQV/R in real life

Patients and Method: between 01-1996 and 11-2003, 254 patients have initiated a saquinavir-ritonavir combination in this prospective cohort. At each visit during therapy, observance, viro-immunologic efficacy and clinical and biological safety were prospectively noted.

Results: Among the 254 patients enrolled in this study, 99% were pre-treated and 85% had received ≥3 ARV sequences. In 50% (n = 127) of cases combination consisted of a baby dose of ritonavir (r)(200 mg/d). The other 127 patients received at least 400 mg/d of ritonavir (R). The 2 groups were comparable at enrolment except for CD4 cells count with a median in SQV/r group = 337 versus 232/mm³ for SQV/R group. At baseline median viral load was 4 log (1.4 - 6.3). At the end of the study there was no difference between the 2 groups with respect to virologic and immunologic responses. Furthermore, in the multivariate analyse the ritonavir posology (as well as baseline CD4 cells count) was not a prognostic factor for virologic response.

- 21% of patients (53) obtained a viro-immunologic response (VL<400 copies/ml and CD4>350/mm³). In OT analyse, the percent of patient with VL<20copies/ml was 42%, 46%, 55%, 74% and 90% of at M6, M12, M24, M36 and M48 respectively.

- 47% (119) stopped because immunologic or/and virologic failure.

The tolerance analysis showed a significant difference in favour of SQV/r as (30/254) 24% of patients receiving SQV/r stopped therapy for intolerance versus (52/127) 41% in SQV/R group (p=0.01).

In both groups,

- 57 patients (22%) stopped therapy because of intolerance (diarrhoea, nausea in particular)

- 14 (5,5%) presented an opportunistic infection or died (all classified C at enrolment)

Discussion and conclusions : The AMM for saquinavir/ritonavir combination, indicates a ritonavir posology of 200 mg/d. Our study tends to prove that in real life this SQV/r combination is indeed as effective as a SQV/R but has a better tolerance.

PP 4.14.**Influence du Passage à l'Association Lamivudine, Zidovudine, Abacavir (TRIZIVIR®) sur l'Observance des Traitements Antirétroviraux.**

Jouglen J, Clement F, Minot A., Lacoste D, Pometan JP.

Service Pharmacie, Service de médecine interne, CHU de Bordeaux, Hôpital Saint-André, Bordeaux, France

Cette étude a pour but de rechercher l'influence sur l'observance du Trizivir®, association diminuant le nombre d'unités prises quotidiennement.

Patients et Méthodes : L'étude s'est déroulée sur 2 ans et concerne 44 patients(1) (H/F = 35/9, âge moyen = 44 ans). Les patients ont reçu pendant un an une trithérapie classique puis l'année suivante du Trizivir®.

L'observance est définie par au moins 10 délivrances d'ARV/ an.

(1) : Patients prenant leur thérapeutique exclusivement dans les pharmacies hospitalières du Chu de Bordeaux.

Résultats :	Période avant Trizivir®	Période avec Trizivir®
Nbre moyen de cp par jour	8,3 (2-22)	2
Nbre moyen de prise par jour	2,186	2
Nbre de patients observants	27 (61%)	32 (72%)*
Nbre de patients non observants	17 (39%)	12 (28%)*

- * : Comparaison des observances moyennes (N = 44, m1 = 9,38, m2 = 10,11 ? = 0,05%) -Test d'égalité des espérances - Supériorité significative de l'observance sous Trizivir®

- Comparaison des patients ayant changé de catégorie (observant devenant non-observant et inversement) : Test Chi-deux : Pas d'évolution significative des comportements individuels.

- Présence ou non d'IP , nbre de lignes de traitements, nbre d'ARV associés avant le passage sous Trizivir : influence non significative sur l'observance.

Conclusion : Le Trizivir® augmente de façon significative l'observance globale, mais on ne peut affirmer que le passage sous Trizivir® entraîne un changement significatif des comportements individuels.

PP 4.15.

Relevance of Lopinavir/r Therapy in Heavily pre-treated Patients

Sola J, Layana E, Alaez JI, Sola I, Uriz J, Castiello J, Reparaz J.

Clinico Universitario, Madrid, Spain

Objetives: To evaluate the efficacy, tolerance and safety of triple therapy with two analogues and Lopinavir/r (LPV/r) in a reference centre for HIV treatment.

Materials and methods: We carried out a retrospective, observational study of HIV patients, where treatment for any given reason with Lopinavir/r was established between January 2001 and February 2004. In all these patients, we determined demographic data, number of previous treatments, date of infection, time period of AIDS, duration of treatment, CD4 count and viremia at the beginning and end of treatment, adverse effects and response to them. Linear multiple regression models were employed for statistical evaluation.

Results: The study included 165 patients, with a mean age of 40.8 years; 69,3% male. IDU 115; 30 were heterosexuals; 16 homosexual, and 5 hemophilic. 46.5% had received more than 5 treatments previously. The mean period of HIV infection was 10.3 years (1-19). 47.3% presented previous AIDS criteria. The mean duration of treatment was 13.4 months (1-36). The initial median CD4 count was 214 (2-1123); final CD4 count 280 (15-1795). Analysis with linear regression revealed: age; (b: 5.287; $p=0.037$), number of changes (b:15,958; $p=0.039$). For each additional year the increase of lymphocytes was 5 cells and by additional change the mean decrease was 16 cells. An adverse effect was present in 11.4% of the patients. The medication was stopped in 3 cases.

Conclusions: There is evidence of immunological response to treatment with LPV/r with an average increase in CD4 lymphocytes of 123 cell/C1 (range, 159-87) and evidence of virological response, with a reduction in viremia of 1.7 log range (2.00-1.3). In regression analysis, both age and number of changes were statistically significant. In general, it was well tolerated presenting some adverse effects in only 11.4% of the patients. Treatment was stopped in only 3 patients.

PP 4.16.**Metabolic Evaluation of Kaletra® (LPV/r)-containing Regimens**

Lafeuillade A, Hittinger G, Geoffroy M, Poggi C, Delbeke E, Jolly P, Lambry V, Philip G.
General Hospital, Toulon, France

Objective: to assess the incidence of lipid and glucose abnormalities in a cohort of patients receiving Kaletra® in their regimen.

Methods: we analyzed lipid levels, glucose levels and HOMA ratio in a series of 159 patients starting a Kaletra®-containing regimen between 04/2000 and 06/2003. These patients were evaluated on a routine basis (real life, longitudinal study) but, in addition, 100 of them agreed to have 1 evaluation after 12 hours fasting (transverse study). At this time, they also completed a self addressed questionnaire on compliance and lipodystrophy. Statistical analysis used the SAS 8.2 software (Cary, USA).

Results: there were 127 men and 32 women with a median age of 41 years. The median duration of HIV infection prior to the introduction of Kaletra® was 9.2 years (8.7-12.0). The median time between the first regimen and the Kaletra®-containing regimen was 5.8 (5.3-6.3) years. Follow-up was available for 1 year in 102 patients and for 2 years in 34 patients. When Kaletra® was initiated, 32.7% of patients were classified as CDC group A, 39.62% as group B and 27.67% as group C. Five patients had known diabetes and 13 received lipid lowering drugs. During follow up, no significant changes in body weight were observed. At the time Kaletra® was initiated, mean (SD) CD4 cell count was 397 (232) cells/ μ l. At the time of the last available evaluation for each patient, a mean gain of 118.72 (226.29) cells was observed. When Kaletra® was initiated, mean (SD) plasma viral load was 4.98 (5.62) log copies/ml. At the time of the last available evaluation for each patient, a mean viral load drop of 1.73 (1.52) log copies/ml was observed. At Kaletra® initiation, mean total cholesterol level was 5.23 (1.62) mmol/l, mean triglycerides level was 2.93 (2.91) mmol/l, mean glucose level was 4.95 (1.23) mmol/l. At the last available evaluation, an increase of 0.46 (1.79) mmol/l in total cholesterol and of 0.90 (4.53) mmol/l in triglyceride levels were observed ($p=0.003$ and $p=0.02$, respectively) but no significant changes in glucose levels were noted. No correlation was found between the CDC group and the development of hypercholesterolemia or hypertriglyceridemia during Kaletra® therapy, when patients with dyslipidemia at Kaletra® initiation were excluded. In the transverse analysis, 54 percent of patients presented cholesterol levels >5.2 mmol/l (<6.22 : 67.01%, $6.22 - 7.77$: 25.77%, $7.77 - 10.36$: 7.22%). Fifty two percent of patients presented triglyceride levels >2.3 mmol/l (<4.4 : 76.26%, $4.4 - 8.25$: 13.40%, $8.25 - 13.20$: 10.31%). Furthermore, 75% of patients had HDL-c <1.45 mmol/l, 15% had LDL-c >4 mmol/l and the mean HOMA index was 2.05 (2.53). There was a statistically significant correlation between increased triglyceride levels or lower HDL-c levels and advanced CDC disease ($p=0.011$ and $p=0.013$, respectively). Compliance was evaluated to be 100% for each prescribed drug in 71-79% of patients. During therapy with Kaletra®, 66.67% of patients considered having morphologic changes, mainly of abdomen and members. There was a trend to a correlation between morphologic changes and hypertriglyceridemia ($p=0.08$).

Conclusion: Kaletra® -containing regimens provide frequent but modest elevations in blood lipid levels. No grade 4 elevations were observed and grade 3 elevations concerned only 10-13% of patients with abnormalities. These lipid changes are correlated with CDC group when evaluation is performed correctly (fasting). No changes on glucose metabolism were observed.

PP 4.17.

Antiretroviral Usage in a Large Metropolitan Area of Northern Italy. Selected drugs and related costs

Manfredi R, Calza L, Chiodo F.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

Aim of our study is to assess a semester of antiretroviral (ARV) prescriptions in the 2 connected outpatient centres in Bologna (Italy), where around 1900 HIV-infected patients (p) are followed, and 1613 (84.9%) received ARV therapy in Jan-Jun 2003. Triple ARV combinations including 2 nucleoside analogues (NA) and 1 protease inhibitor (PI) or 1 non-nucleoside inhibitor (NNRTI), or 3 NA, were given to 67.9 of p, while in 18.3% of p a double NA association was still used, and the remaining 13.8% of p received >3 drugs. The most prescribed NA associations was AZT-3TC, followed by d4T-3TC, and d4T-ddI. The PI combination prevailed over the NNRTI one, and a triple NA combination (39%, 28%, and 9%, respectively). Among NA (13409 monthly packages), d4T remained the most used agent (4128), followed by co-formulated AZT-3TC (2851), 3TC (2844), ddI (2049), AZT (524), TDP (367), co-formulated AZT-3TC-ABC (366), ABC (236), and ddC (44). When considering PI (4162 monthly packages), lopinavir/r (1611) prevailed over indinavir (927), nelfinavir (876), saquinavir hg (308), ritonavir (288), saquinavir sg (108), and amprenavir (44). Among NNRTI (3113 monthly prescriptions), nevirapine and efavirenz had a comparable usage rate (1604 and 1509 packages, respectively). Among highly effective triple ARV combinations, significant differences are evident according to costs, with d4T-TDP-lopinavir/r as the most expensive PI-based association (870 Eur/month), vs AZT-3TC-saquinavir sg/r (547 Eur/month). When considering NNRTI-based ARV therapy, d4T-TDP-efavirenz is the most expensive (642 Eur/month), vs AZT-3TC-nevirapine (452 Eur/month). Finally, the fixed AZT-3TC-ABC combination is borne by a comparable monthly cost of 515 Eur. Eight years after HAART introduction, a very broad spectrum of variables influences the choice of the best ARV combination for each treated p, including therapeutic background, resistance, toxicity, adherence, pill burden, and also expenditures. Among 1st-choice regimens (including efavirenz or lopinavir/r), this last option is borne by significantly increased expenses (368 vs 232 Eur/month), when limiting this observation to the 3rd agent, to be added to 2 backbone NA. Given the availability of 18 compounds and the introduction of novel agents (enfuvirtide, novel NA, PI, and NNRTI compounds and formulations), a correct balance of expected long-term efficacy and tolerability should be weighted also against scheduled costs, in order to give the best allocation for available ARV drugs, and health care resources.

PP 4.18.**A Comparison of the Two First-line Recommended Antiretroviral Regimens for Naïve HIV-infected Subjects**

Manfredi R, Calza L, Chiodo F.

Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

The 2003 international guidelines for antiretroviral management consider lopinavir/ritonavir- or efavirenz-based highly-active antiretroviral therapy (HAART) as the first-line choice for HIV-infected antiretroviral drug-naïve patients, but no randomized comparative studies exist between these two therapeutic strategies, as to efficacy and safety. The most relevant efficacy and tolerability parameters of lopinavir/ritonavir- and efavirenz- based HAART, were evaluated in 82 antiretroviral naïve patients followed since the year 2002 in an open-label observational single-centre study. Forty-three consecutive patients treated with lopinavir/ritonavir plus two nucleoside analogues, were compared with 39 subjects who received efavirenz plus two nucleoside derivatives, selected from all available molecules. The two patient groups were comparable at baseline as to demographic and epidemiological features, as well as mean viremia (4.4 ± 1.4 , versus 4.3 ± 1.7 Log₁₀ HIV-RNA copies/mL, for lopinavir-ritonavir and efavirenz, respectively), but a prior or concurrent full-blown AIDS ($p < .03$), and/or a lower mean CD4+ lymphocyte count ($p < .005$) were found among patients given lopinavir-ritonavir. During the 9-28-month follow-up reached until now, laboratory examination showed a comparable virologic response (as to time and rate of viral decay and suppression), in presence of only one case of virologic failure in the efavirenz group, versus no cases in the lopinavir-ritonavir group (n.s.). Notwithstanding the significantly lower mean initial CD4+ cell count, lopinavir-treated individuals achieved a more rapid and elevated immune recovery ($p < .03$ versus efavirenz-treated patients). The overall need of regimen interruption or substitution attributable to toxicity, untoward events, insufficient patients' adherence, or laboratory failure, was comparable in the two study groups, but the observed mid-term toxicity proved significantly different, since lopinavir-treated patients experienced dyslipidemia in over 45% of cases (hypertriglyceridemia in over one third of patients), versus nearly 10% of cases belonging to the efavirenz group ($p < .001$). Early (first month) interruptions due to a poor tolerability rate proved similar: 7 patients were recorded in the lopinavir-ritonavir group, versus 6 episodes among efavirenz-treated patients, although short-term untoward events predominantly involved the gastrointestinal tract for lopinavir-ritonavir, and the central nervous system for efavirenz ($p < .001$). Our experience conducted on 82 antiretroviral-naïve subjects treated with a lopinavir-ritonavir or an efavirenz-based HAART, showed a comparable virologic response, although an apparently more potent and rapid immunologic recovery was seen in the lopinavir group (even taking into account a more severe initial immunodeficiency in these last patient group). On the other hand, while efavirenz-treated patients experienced more rare adverse events, and benefited from a low pill burden, however the rate of early treatment interruptions tested similar in the two study groups. On our opinion, international guidelines propose either lopinavir-ritonavir or efavirenz as equivalent first-line treatment of HIV disease, but in absence of randomized comparative studies the selection of lopinavir- versus efavirenz-based regimens should have to consider the initial immunological and disease status. Further data are strongly warranted on long-term outcome, viral resistance burden, and tolerability issues of these two first-line antiretroviral regimens. Given the profoundly different cost of these two therapeutic strategies, an appropriate pharmaco-economic assessment seems also recommendable.

PP 4.19.

Advances in Antiretroviral Therapy of HIV Infection

Akomiah P, Bio T,

University of Cape Coast, Cape Coast, Ghana

Progress in antiretroviral therapy has resulted in both achievements, with the dramatic reduction in morbidity and mortality, and new challenges, with the limitations in tolerance and activity of available antiretroviral regimens. As a result of these considerations, recommendations on when to start therapy in asymptomatic, chronically infected individuals have shifted to a more conservative approach. The immediate future will be marked by the availability of new assays, particularly for virus resistance testing, the availability of new drugs (both from existing classes and drugs acting on new virus targets), and the evaluation of new therapeutic concepts and strategies.

On a global scale, the recent impressive therapeutic gains have only benefited 10 % of those infected in the South of the world the epidemic is reversing decades of development and widening the gap between rich and poor nations. Africa carries a staggering 75% of the global burden of HIV/AIDS. Life expectancy at birth has decreased markedly in many African nations; experts project that life expectancy in Botswana, which has one of the highest infection rates worldwide, will be approximately 29 years by 2010.

The dramatic inequalities between rich and poor nations in caring for persons living with HIV/AIDS highlight the moral imperative to develop strategies to increase access to life-saving treatments for the majority of infected people.

PP 4.20.**Interruption Thérapeutique Programmée chez l'Enfant Infecté par VIH.**

Monpoux F., Tricoire J., Lalande M., Reliquet V., Thuret I.

CHU de Nice, Toulouse, Montpellier, Nantes, Marseille, France

L'interruption thérapeutique programmée (ITP) est pratiquée dans 3 situations chez l'adulte infecté par VIH. 1- au décours d'une primo-infection, 2- chez des patients stables immuno-virologiquement, 3- lors d'une " impasse thérapeutique " afin d'obtenir la ré-émergence de quasi espèces sauvages prédominantes. Les conséquences de ces différentes pratiques sont actuellement discutées. Nous avons souhaité analyser les pratiques de pédiatres français en matière d'ITP chez l'enfant.

Patients et méthodes : Une fiche de recueil comportant des renseignements épidémiologiques, cliniques, immuno-virologiques et thérapeutiques a été adressée aux pédiatres responsables du suivi des enfants infectés de 5 CHU Français. Nous avons distingué les ITP pour " impasse " immuno-virologique (Wash-Out [WO]) et celles pour " vacances thérapeutiques [VT]).

Résultats : 24 enfants de 10.5 ans d'âge median (19 filles) tous contaminés par transmission materno-fœtale (TMF) ont été recensés. Dix ITP étaient proposées pour WO, 14 pour VT. Tous les enfants avaient préalablement été exposé à au moins 1 analogue nucléosidique, 46% à au moins 1 non nucléosidique, 54% à au moins 1 inhibiteur de protéase. La durée mediane d'ITP est de 40 semaines (WO : 28, VT : 48 p=NS). A ce jour, 14 patients poursuivent leur ITP (WO : 3, VT : 11). Aucun enfant n'a présenté d'évènement classifiant durant l'ITP. La CV mediane à l'ITP est de 4.14 log10 (WO : 4.34, VT : 3.4 p = 0.004) Le pourcentage median de CD4 est de 26% (WO : 24.5, VT : 28, p= 0.06). L'accroissement maximale de CV est de 1.26 log10 non significativement différent dans les 2 groupes (WO : 1.26, VT : 1.14). La perte maximale de cellules CD4 est de 32.5% (WO : -46%, VT : -29% p= NS)).

Conclusions : L'ITP proposée pour WO ou VT est de pratique peu courante en pédiatrie. Sous réserve d'une surveillance attentive, aucun élément classifiant n'a été diagnostiqué dans notre série. Cependant, l'élévation massive de la charge virale et la perte importante de CD4 constaté nous conduit à ne proposer cette attitude que sous strict contrôle d'une équipe expérimenté. Des analyses complémentaires (génomiques) sont actuellement en cours.

PP 4.21.

Efficacy Evaluation of Combined Chemoprophylaxis of Vertical HIV Transmission

Shostakovich-Koretskaya LR, Hozhilo II, Chykarenko ZA, Cherginets AV.
Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine

The background: The problem of perinatal HIV transmission is one of the medical priorities in Ukraine due to the highest spread rate of HIV infection among pregnant women in our country (0,51% of pregnant are HIV infected and newly diagnosed cases are 0,4% due to the regional studies; among infants 96,7% were infected perinatally).

Objective of our study: to evaluate the efficacy and economical value of the suggested protocol of combined double perinatal transmission prevention.

The materials and methods: under the investigation there were 30 pregnant women with serologically confirmed HIV infection (mean age 28,5 years old) and their 30 newborns (with positive HIV serology at birth). The prophylaxis of vertical transmission was performed according to the suggested scheme: ZDV for pregnant women since 36th week of pregnancy (300mg tid) and during delivery (300mg every 3 hours) and NVP for newborns during first 72 years of life (2mg/kg once). This group was compared with the similar group of 30 HIV-positive pregnant women and their newborns. None of the children in both groups received breast feeding. The HIV infection status in infants was tested serologically at the age 6, 9, 12 and 18 month by ELIZA and Western Blotting methods.

Results: this protocol was shown to be 93,3% effective: the decrease of the frequency of perinatal transmission was from 26,8% in untreated group down to 6,7% in treated one. The cost of the treatment was 16,5 - 75 US\$, depending on body weight and delivery period length. The usage of this two antiretroviral drugs for the prophylactic regimen was based on the different mechanism of action, that was expected to increase the efficacy of the regimen.

Conclusion: considering the high risk of perinatal HIV infection in children in regions with complicated economical situation, the suggested protocol of perinatal transmission prevention can be economically valid and effective for prophylaxis of perinatal HIV transmission.

PP 4.22.**A Pilot Study Evaluating the Efficacy and Safety of a Bioadhesive Buccal Tablet of Miconazole 50 mg (Miconazole Lauriad™) in HIV Positive Patients with Oropharyngeal Candidiasis**

Dupont B, Dellamonica P, Datry A, Consigny PH, Kirstetter M, Poizot-Martin I, Meyohas MC, Chaumont C, Crougths T, Lafeuillade A.

Hosp Necker, Hosp Pitié Salpêtrière, Hosp Bichat, Private institution, Hosp Saint Antoine, BioAlliance Pharma, Paris; Hosp Archet, Nice; Hosp Sainte Marguerite, Marseille; Hosp Chalucet, Toulon, France

Miconazole Lauriad™ is a bioadhesive buccal tablet which provides a prolonged release of miconazole. It has been demonstrated an excellent tolerance and bioadhesion (mean = 15h) in healthy volunteers and a time above MIC (minimal inhibitory concentration) of *Candida albicans* of 7 hours.

The purpose of this study was to evaluate the efficacy and safety of miconazole Lauriad™ in HIV positive patients suffering from oropharyngeal candidiasis.

This multicenter, open-label, non comparative phase III trial assessed the efficacy and safety of a 50 mg once-daily topical regimen of miconazole Lauriad™ in HIV-positive patients with an oropharyngeal candidiasis. Candidiasis was clinically documented and confirmed by fungal culture before inclusion. Patients were treated for 14 days and those who exhibited a clinical response were followed up to an additional month to evaluate the relapse rate. Primary efficacy was defined by lesion disappearance or decrease of more than 50% of lesion extension after 14 days of treatment. Secondary outcomes included clinical response at day 7, presence/absence of *Candida* species on fungal culture, safety, duration of tablet adhesion and compliance. Results : a total of 25 patients (17 males and 8 females) were included (intent-to-treat-population, primary population for the safety analysis) with median age of 41 years and median CD4 number of 112 cells/mm³ (range 1 to 669). 68% of the ITT population had a stable HIV treatment at pre inclusion. 19 patients were evaluated for efficacy, all had *Candida albicans* in the fungal culture at inclusion time and 1 of them had an additional species (*Candida glabrata*). Miconazole Lauriad™ showed a 94.7% clinical efficacy (18 of 19 patients) after 14 days of treatment. Fungal eradication (negative fungal culture) was seen in 31.6%. Clinical response at day 7 was 89.5% (17 of 19 patients). The time duration of tablet adhesion was longer than 12 hours in 73.7% of patients. The relapse rate at day 45 was 36.8% (7 patients of 19). The absence of plasmatic concentration of miconazole at day 7 of treatment demonstrated that miconazole Lauriad™ acts only locally. Miconazole Lauriad™ was well tolerated with only three non serious adverse events reported to be related to treatment (2 gastro intestinal disorders and one dysgeusia). In conclusion, miconazole Lauriad™ is safe and provides an innovative once-daily topical treatment of oropharyngeal candidiasis in immunocompromised patients.

PP 4.23.

Algorithmic Guidelines in the Management of Dysphagia and Odynophagia in Immune- compromised Patients at Kigali University Hospital

Murenzi FC, Van Den Ende J.

National University Of Rwanda, Kigali, Rwanda

Introduction

Algorithm format of management of various symptoms has been proposed for quite a longtime but their effectiveness and efficiency has not been determined yet. The objective of our clinical trial was to identify clinical guidelines in the management of dysphagia and odynophagia in the suspected immune-compromised patient at KUH converting them into algorithm to validate Kigali university hospital algorithm and to compare them with those suggested by MSF and WHO.

Material and method

The clinical trial was carried out prospectively from April to June 2002 in the department of internal medicine Kigali university hospital on 110 patients. All patients with dysphagia and odynophagia and were suspected immune-compromised according to WHO criteria were included in our study. Algorithm was designed from the views of the practicing clinicians in KUH. This algorithm was validated and compared with those suggested by MSF and WHO. The EPI-INFO version 6.04 was used for analysis.

Results

110 patients were included in our study, the common age group affected was 35-44 accounting for 39%, and Candidiasis was the most frequent diagnosis. Esophageal candidiasis accounting for 68% and esophageal candidiasis 11%. 74% of the patient improved on treatment while 25% died. 110 (100%) followed certain pathways on the KUH algorithm as compared to 100 (90%) and 88(80%)who followed certain pathways

Respectively. Final diagnosis was obtained when the KUH, MSF, and WHO algorithm were applied in 108(98%), 100(90%), 88(80%) respectively. The difference in mean of the time elapsed before the start of the actual treatment for the different algorithm (KUH, MSF and WHO) was not statistically significant.

Conclusion

Candidiasis was the most frequent cause of dysphagia and odynophagia, in spite of a completely different design the mean time elapsed until effective treatment for KUH, MSF, WHO was almost similar, two false negative for KUH was found neither false positive nor false negative for MSF and WHO. More simple algorithm lack fit and efficacy.

PP 4.24.**Filling Treatment of Facial Lipoatrophies by a Biodegradable Product in HIV Patients**

Carbonnel E, Claudy A.

Hospital E. Herriot, Lyon, France

Lipoatrophies are a frequent complications of anti-HIV treatment, espasally of anti-protease inhibitors. The prevalence of such lipoatrophies is 60% after 18 months of anti-HIV treatments. The incidence is 11.7/100 patients-years. 81 patients entered the study. They were treated with a reticulated polyacrylamide copolymer (Outline, ou Eutrophyl laboratory Procytech) approved by the European Community. The product is degraded by enzymes, releasing low molecular weight polyacrylamide chains, without monomers, therefore without toxicity. 4ml of the product were injected intradermally in each site of the cheeks and temples. The number of sites injected varied from 3 to li. Exclusion criteria included coagulation disorders, acute bacterial infection, HSV infection and auto-immune diseases.

Ten patients were evaluated clinically and by measuring the cutaneous fold and the dermal thickness by echography before treatment and 6 months after treatment. The results showed a persistence of the filling in all patients without any side effects, notably no granulomatous reactions, over a mean time of 9 months (range 6-12 months). The cutaneous fold and the dermal thickness, as measured by echography, doubled in the 10 patients evaluated.

In conclusion, the reticulated polyacrylamid copolymer permitted a sustained correction of the lipoatrophy in HIV patients without side-effects. Long term results remain to be evaluated.

PP 4.25.

Use of Pyrimethamine-Sulfadoxin in Treatment of Cerebral Toxoplasmosis in HIV Infected Patients

Gomez JE, Alvarado F, Hernandez C, Cuervo S, Saravia J.

Centro Investigaciones biomedicas, Universidad del Quindio, Colombia

Background: in Colombia and other countries, pyrimethamine or sulfadiazine alone are not available. The only pyrimethamine-sulfonamids combination that can be obtained is Pyrimethamine plus sulfadoxine. Sulfadoxine is a long lasting sulfonamids and there are not publications that have reported their use in cerebral toxoplasmosis (CT).

Setting: "Hospital San Juan de Dios" in Bogotá (Colombia) during the period January 1995 to March 1999.

Methods: retrospective study of clinical charts.

Patients: 18 HIV patients with clinical diagnosis of cerebral toxoplasmosis (CT).

Results: mean age in patients was 35 years (range: 24-46); 16 were men and 2 were women. CT was the first clinical condition of AIDS in 66% of patients. IgG anti-Toxoplasma was positive in 15 of 16 patients (93%). Treatment with a combination of Clindamycin plus pyrimethamine _sulfadoxine resulted in complete clinical improvement in 13 cases of 15 cases (86%). Death occurred in 3 cases (25%) and this was probably associated with a long evolution previous to treatment. Allergic reactions occurred in 5 cases (25%), one of them presented a Stevens-Johnson reaction.

Conclusions: treatment with a combination of clindamycin plus pyrimethamine-sulfadoxine was effective in a similar rate than reported for pyrimethamine-sulfadiazine.

PP 4.26.**Therapeutic Drug Monitoring (TDM) of Nelfinavir (NFV): Recommendations for Optimization**

Laurent S, Sigrist H, Solas C, Poizot-Martin I, Chadapaud S, Frixon-Marin V, Lafeuillade A, Dhiver C, Moreau J, Pichancourt G, Ravaux I, Cohen Valensi R, Ruer J, Lacarelle B.

Timone Hospital, Sainte-Marguerite Hospital, Conception Hospital, Nord Hospital, Marseille; Chalucet Hospital, Toulon; Henri Duffaut Hospital, Avignon; Martigues Hospital, Martigues, France

Introduction: TDM of NFV may be beneficial in individualizing regimens: low plasma levels of NFV + metabolite M8 (<1000 ng/ml) have been related to virological failure. Moreover, NFV plasma concentrations are highly variable and decreased without concomitant intake of a high fat meal. The purpose of this study was to point out the pertinent information required for a good interpretation and optimization of NFV TDM.

Methods: A prospective, observational and multicenter study was performed from November 2003 to February 2004 by analyzing data from the routine monitoring of patients receiving NFV as part of their current antiretroviral (ARV) regimen. Data collected on the TDM request form were: NFV dose, time between the last drug intake and the sample collection, ARV and other comedications, hepatic status. Trough plasma concentrations of NFV+M8 were assessed 12 ± 2 hours after the last dose and measured by a validated HPLC assay.

Results: Fifty-five samples were analyzed from 40 patients during the follow-up period. Missing data collected from the request form were: NFV dose (7.3%), time between the last drug intake and the sample collection (5.5%), ARV (12.7%) and other (83.6%) comedications, hepatic status (56.4%). Median NFV and M8 Ctrough (CV%, range, n) were 1221 ng/ml (69.7%, 103-3719, 46) and 437 ng/ml (86%, 114-2377, 46), respectively. 40% of the patients had a NFV+M8 Ctrough below the 1000 ng/ml recommended threshold with a median value of 369 ng/ml (range: 103-726) for NFV and 166 ng/ml (range: 114-310) for M8.

Discussion: 40% of the patients had a NFV+M8 Ctrough below the recommended threshold value. Several factors affect NFV+M8 plasma concentrations such as the absence of high fat meal associated to the NFV intake, drug-drug interactions or adherence problems. Therefore, it seems difficult to clearly identify the reasons of low NFV+M8 levels. Our results underline the need to educate and inform both patients and medical team: 1) on the impact of food on NFV concentrations, and 2) on the relevance of the information indicated in the TDM request form. A better utilization of TDM would allow improvement of therapeutic outcome predominantly by decreasing the percentage of patients with low NFV plasma concentrations.

PP 4.27.

How a Warning can Avoid a Medicine Error

Boivin H, Nau P, Andre V, Rouleau A.

Pharmacy CHRU Tours, - Hospital Bretonneau, France

A new dosage of lamivudine (Epivir) 300mg once a day is on the market but the box is strictly identical with Epivir 150mg. So, a risk of error exists.

To manage to change the box in order to avoid any risk of error when dispensing and taking a medicine by patients.

We have alerted professionals at different levels:

- Centre Regional de Pharmacovigilance (CHRU Tours)
- Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps)
- Laboratories Glaxo-Smithkline

A change of the box of Epivir 300mg: a blue strip at the the bottom of the box and dosage written in red to distinguish between Epivir 150mg and Epivir 300mg.

A rapid description of a significant matter (in this case, the box) caused a change of the appearance of the box, less than one year in order to avoid any risk of error.

We have made other requests for additional changes.

Do not hesitate: even a single intervention can lead pharmaceutical laboratories to important modifications

PP 4.28.**Comparison of Efficacy of Two Interventions to Enhance Adherence to Antiretroviral Therapy (HAART)**

J. Benkimoun J, Gnamien S, Dupont C, Chaltiel L, Aubry N, Le Mercier F, Rouveix E, Lebas-Certain M. Department of Pharmacy & Department of Internal Medicine, Hôpital Ambroise Paré (AP-HP), Boulogne, France

PURPOSE : The aim of this study was to compare the efficacy of two interventions - Cognitive, Behavioral and Affective Strategy (CBAS) versus Cognitive Strategy Only (CSO) - both of them individual-level, leaded by pharmacists, to enhance medication adherence to HAART. CSO give tailored information about HAART to each patient. CBAS is a therapeutic education intervention, on medical prescription, permitting monitor side effects and costumised adherence feedback.

PATIENTS AND METHODS : A prospective study was conducted, between June 2002 and April 2004, to compare two groups of outpatients selected by chronological arrival to the pharmacy : 1) group CBAS : 2-sessions (2x45min) CBAS intervention (n=18); 2) group CSO : 1-session (15min) CSO intervention; both of them in addition to standard of care (n=18). Both groups were stratified to initiation or simplification versus switch of HAART. Adherence was assessed on March 2004 by patient self report using "adherence rule", and pharmacy refill. Outcome measures included 6 months follow up (M0 to M6) of virological and immunological responses to HAART. Data of barriers to and cause of adherence and tolerance were collected.

RESULTS: This study suggests that the stated level of adherence was high in both groups : over the study period of adherence, the patients said they had taken 99% of doses during the last four days. During the six months follow up, HIV RNA significantly decreased in both groups. At M6, the proportion of patient with HIV RNA < 200 copies/ml remained similar in both groups.

CONCLUSION : Since there is no gold standard for determining treatment adherence, it is important to combine several methods to minimize errors of results. CBAS and CSO interventions are comparable in efficacy for increasing adherence to HAART. Difference should be better explored in terms of quality of life.

PP 4.29.

Cultural Adaptation and Validation of a Lipodystrophy Quality of Life Questionnaire

Duracinsky M, Cervoni J, Vincent V, Lascoux C, Sereni D, Molina JM, Acquadro C, Wu A, Chassany O. Hopital de Bicêtre; Hopital Lariboisiere, Hopital Saint-Louis, Paris; MAPI Research Institute, Lyon, France; Johns Hopkins University, Baltimore, USA

Background: Lipodystrophy may have a great impact on quality of life (QoL). Current HIV specific instruments do not measure this impact. We performed a cultural adaptation and psychometric validation in French of a new lipodystrophy specific instrument "Assessment of Body Change and Distress" (ABCD). Methods: ABCD consists of 3 parts: signs of lipodystrophy (6 items), global satisfaction (1 item) and 20 items evaluating QoL. Items were generated in US. Our study consisted of 2 parts: 1/ Cultural adaptation of ABCD in French through forward-backward methodology and cognitive debriefing; 2/ Psychometric validation in a survey in comparison with specific (MOS-HIV) and generic (SF-12) QoL questionnaires. Results: The approach of French patients was to some extent different from US patients, and needed cultural adaptation of several concepts. 155 HIV French out-patients (143 with lipodystrophy) from 2 Parisians hospitals and 1 general practice were included. Mean age was 43 ± 10 yrs (71% men, 50% homosexual). 32% of patients had a grade C (CDC). Mean duration of HAART was 4.5 ± 1.7 yrs. ABCD QoL score (0-100) was more impaired in women (49 ± 23) than men (61 ± 21). Discriminant validity: QoL score decreased according to the number of sites with lipodystrophy, ranging from 85 ± 16 (none) to 42 ± 10 (6 sites), $p < 0.001$, and according to whether patients were thinking about plastic surgery or not, from 68 ± 20 (never) to 33 ± 13 (always), $p < 0.001$. Internal consistency was high (Cronbach $\alpha = 0.94$). Factorial analysis yielded a 4-factor structure. Convergent validity: the highest correlations were between ABCD QoL and health distress and social dimensions of the MOS-HIV ($r > 0.6$) and with the mental component of the SF-12 ($r = 0.65$). Conclusion: The psychological and social distress related to the body changes must be measured in clinical trials, to make sure that life is not lengthened at the expense of its quality. ABCD questionnaire is a validated questionnaire which can now be used in French.

PP 4.30.**Persistent Low Viremia and Future Treatment Options**

Dyner T, Cafaro V, Chow V. Shared Perspectives on Therapies, San Francisco, USA

BACKGROUND: The potential loss of future treatment options in HIV infected patients with low level viremia has prompted some clinicians to change regimens when viral loads were above detectable levels. With this concern and the need to treat HIV infection for decades, we evaluated a cohort of low viremic patients on stable treatment regimens. **METHODS:** Charts of 18 patients were reviewed for CD4s, viral loads, and at least 3 resistance tests over a 2 year period. **RESULTS:** Patients were on these various regimens an average 62 months (range 25-88). The baseline average CD4 and HIV-bDNA for the current regimen was 415 cells/mm³ (range 38-700) and 4.2 log₁₀ copies/mL (range <2.7-4.8 log₁₀), respectively. Change in CD4 count from baseline to March 2004 averaged -1.17 cells/mm³ while the change in HIV-bDNA averaged -0.27 log₁₀ copies/mL. There was an average increase in point mutations of 1.6; however, 1/3 of patients developed no new mutations. Phenotypic fold change increased in 6/18 patients. **CONCLUSIONS:** This cohort of patients on a stable HIV treatment regimen of at least 5 years, maintained immunologic competence with persistent low level viremia. In patients electing to maintain a stable regimen despite low level viremia, our data suggest that future treatment options may not be impaired.

PP 4.31.

Impact of Highly Active Antiretroviral Therapy (HAART) on Blood Pressure (BP) in Patients with HIV Infection. A prospective study in a cohort of naïve patients

Palacios R, Santos J, Castell E, González M, Ruiz J, Márquez M. Hosp Virgen de la Victoria. Campus Teatinus, Málaga, Spain

Background: although HAART has been related to high blood pressure (HBP), the few available data are controversial.

Objective: to assess the impact of HAART on the BP of naïve patients after one year's treatment and to analyse the factors related to hypertension.

Methods: prospective study of 95 HIV-infected patients starting HAART in 01/01-10/02 and following the same regimen for 48 weeks. Patients were excluded if they were pregnant, breast feeding, or were alcohol or illegal drug abusers. Clinical, anthropometrical, laboratory data, and systolic and diastolic BP (SBP and DBP) were recorded at the start of the study and after 48 weeks. HBP: The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. High pulse pressure (HPP): ≥ 50 mmHg. Dyslipidaemia: National Cholesterol Education Program. Overweight: BMI > 25 kg/m². Statistic program: SPSS 11.0.

Results: 128 patients started HAART, 116 fulfilled the inclusion criteria, 21 were excluded due to a change in their HAART regimen or because they were lost to follow-up. 95 patients completed the study. Men 78, mean age 39.9 years. Aids: 44.2%. Smokers: 68.1%. Baseline: HBP 7.4%, BMI 23.1 kg/m², CD4 165.4/ml, HIV VL 5.19 log₁₀. PI: 48.4%. Week 48: HBP 23.1%, HPP 43.9%, lipodystrophy 40.0%. SBP, DBP and PP increased (124.6 vs 116.6 mmHg, 77.7 vs 72.8 mmHg, 46.9 vs 43.8 mmHg; $p < .001$). HBP was related to age (44.4 vs 37.0; $p = .001$), BMI [26.6 vs 23.9 kg/m²; $p = .005$. OR (overweight) 2.4. CI95% 1.09-5.3; $p = .025$], BMI increase (2.8 vs 1.1 kg/m²; $p = .008$), baseline lipids [TG 216.8 vs 150.7 mg/dl; $p = .005$. OR (hypercholesterolemia) 2.9. CI95% 1.4-5.9; $p = .01$] and baseline BP (SBP 128.1 vs 112.3, DBP 79.7 vs 71.0, PP 48.4 vs 41.3; $p < .01$), but only BMI increase (OR 1.17. CI95% 1.07-1.2; $p = .0003$) and baseline TG (OR 1.01. CI95% 1.001-1.01; $p = .01$) were significant in Cox regression. HPP was associated with baseline SBP and PP (121.2 vs 113.6 mmHg; $p = .048$. 48.8 vs 40.7; $p = .002$), SBP increase (18.7 vs 0.4 mmHg; $p = .0001$), baseline HPP (OR 1.8. CI95% 1.1-3.0; $p = .014$) and HBP at 48 weeks (OR 2.42. CI95% 1.5-3.9; $p = .001$) but baseline HPP (OR 2.27. CI95% 1.1-4.6; $p = .02$) was the only associated factor in Cox regression.

Conclusions: BP increased after 48 weeks HAART, leading to an important prevalence of hypertension. Although it was associated with traditional risk factors, HAART-related metabolic disorders may contribute. A longer follow-up of patients on HAART will reveal more information about the true role of HAART and its metabolic consequences on high blood pressure. Whatever the case, as high blood pressure itself is an important cause of increased cardiovascular risk in HIV patients on HAART, it should be periodically measured and treated when necessary.

PP 4.32. HIV Positive Patients' Perspectives about their Adherence to Antiretroviral Therapy

Morillo García A., Gasch Illescas A., Valencia Martín R., Aldana Espinal JM, Conde Herrera M. Virgen del Rocío Hospital, 41013 Sevilla

Introduction: this study has been motivated by the critical importance of adherence on the effectiveness of antiretroviral therapy, the shortage of interventions focused on the improvement of compliance and the lack of qualitative studies in our country in relation with this subject. The objective is to explore the factors, perceived by HIV positive patients, that influence their adherence to antiretroviral therapy.

Methods:

Design: qualitative research method using semistructured interviews carried out between July and August 2002.

Setting/participants: the study included 18 HIV positive patients treated with antiretroviral therapy attended at Infectious Diseases Department, in the Virgen del Rocío hospital in Seville and at two Drug Addict Centres, in Alcalá de Guadaíra.

The interview examined, throughout the PRECEDE model, the factors that predispose, facilitate and reinforce the adherence to antiretroviral therapy. The results were triangulated with experts and other quantitative and qualitative studies.

Results: the predisposing factors that affect the compliance to antiretroviral therapy are the patients' perceptions of their illness and medication support. Some of the barriers described were the treatment characteristics and external factors, as the lack of social support and drug addiction. The patient-doctor relationship and the family support are considered the most important facilitator and reinforcing elements. The physical and psychological benefits due to the medication are also crucial to improve their adherence.

Conclusions: a multidisciplinary effort is required. It's an absolute priority to strength and promote the bonds between physician and patient, exchanging views and participating in decision-taking processes. It's essential to reinforce their adherence, not only with HIV positive people, but also in other long-term diseases.

Keywords: adherence, highly active antiretroviral therapy, reinforcement, physician-patient relationship, PRECEDE model, qualitative study.

PP 4.33.

Patients-reported Factors Influencing Adherence to Antiretroviral Therapy

Montana M, Darque A, Ravaux I, Gallais H, Gensollen S, Bongrand MC, Timon-David P. Hospital Pharmacy, Infectious Diseases Wards, Conception Hospital, Marseille, France

Prospective study over a 6-month period, from August to February 2004, based on a self-questionnaire filled only once by patients, in order to explore factors that influence adherence to antiretroviral therapy and major side effects of treatment. A total of 250 questionnaires were filled. Number of patients treated by 3, 4, or 5 antiretroviral drugs was 222, 27, and 1, respectively. Overall respect of treatment was estimated satisfactory, intermediate, and not satisfactory in: 74%, 22%, and 4% of patients, respectively. Patients' anteriority or nature of treatment (presence of protease inhibitor) did not significantly modify these results.

Classification of observance-limiting factors was: adverse events (30% divided in asthenia 7%, diarrhea 4%, weight problem 5%, muscular or bone pain 4%, abdominal-pain 30%, nausea and vomiting 3%, somnolence or excitement 3% and fever 1%), pill size (22%), alimentary constraints (15%), number of pills per administration (15%), total number of pills per day (13%), and other factors (5%). Patients' preference was to take more pills if it allows decreasing the number of daily administrations, rather than to increase the number of administration and have fewer pills to take at the same time (64% for all patients and patients with good observance, and 56% for patients treated with a protease inhibitor). Compliance was mainly limited by adverse events rather than anteriority or nature of treatment. Availability of once-a-day treatment and providing support / information to patient can be paths to improve compliance. Pill size and galenic improvement (formulation, prolonged liberation) are technical parameters on which pharmaceutical companies have to continue development since the number of antiretroviral associations currently feasible on a once-a-day basis is limited.

PP 4.34.**Antiretroviral Prescriptions Proved Significant Different Between the Two Outpatient Centres of a Metropolitan Area in Northern Italy: an analysis of economic correlates**

Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

The knowledge of profile and trend of antiretroviral prescriptions is strongly warranted, in order to better allocate pharmacologic resources. A comparison of electronic databases of antiretroviral drug prescriptions in the two linked HIV outpatient centres of Bologna (Italy), where around 1,900 HIV-infected patients, are followed, has been carried out. As a whole, the study regarded 1,644 patients (86.5% of the overall cohorts), who received anti-HIV therapy during the year 2003. Triple combinations including two nucleoside/nucleotide analogues and one protease inhibitor or one non-nucleoside inhibitor, or three different nucleoside/nucleotide analogues, were given to 68.2% of patients, while in 18.2% of cases a double nucleoside analogue association was still used, and the remaining 13.6% of patients received more than three drugs. On the whole, a protease inhibitor-based antiretroviral treatment still prevailed over the non-nucleoside-based one, and the isolated nucleoside/nucleotide analogue one (38%, 31%, and 10%, respectively). Among nucleoside/nucleotide analogues, lamivudine, zidovudine, stavudine, and tenofovir were prescribed with a significantly greater frequency at the first HIV outpatient unit ($p<.001$ to $p<.03$), while abacavir and co-formulated zidovudine-lamivudine-abacavir were administered more frequently at the second city unit ($p<.02$ to $p<.05$). When considering protease inhibitors, saquinavir hard gel and nelfinavir were more commonly used at the first HIV outpatient centre ($p<.001$), while saquinavir soft gel was more common at the second unit ($p<.04$), and non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz and nevirapine) had a comparable prescription rate. Since the prescription of antiretroviral therapy is performed by the same medical equipe since June 2002, reasons for such a significant differences are expected to be linked to specific patient features: a greater prevalence of sexually-transmitted HIV infection is evident at the first outpatient centre, compared with a greater i.v. drug addiction among patients enrolled by the second city unit ($p<.01$). Moreover, a longer history of antiretroviral therapy with more frequent treatment changes was recognized at our first unit, compared with the second one ($p<.004$). Dealing with the different antiretroviral strategies, we have to take into account both efficacy and safety, and related costs, too. Among the different available highly active antiretroviral therapy (HAART) regimens, significant differences are evident according to expenditures, with stavudine-tenofovir-lopinavir/ritonavir as the most expensive protease inhibitor-based regimen (870 Euros/month), versus zidovudine-lamivudine-saquinavir soft gel/ritonavir (547 Euros/month). When assessing non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy, stavudine-tenofovir-efavirenz is much more expensive (642 Euros/month), as opposed to zidovudine-lamivudine-nevirapine (452 Euros/month). The fixed zidovudine-lamivudine-abacavir combination (containing only nucleoside analogues) has comparable costs (515 Euros per month). Eight years after the introduction of HAART as the standard of care of HIV disease, a broad spectrum of variables continue to influence the choice of a "tailored" antiretroviral therapy for each treated patient, including therapeutic background, resistance, toxicity, compliance, pill burden, and also expenditures. Even between the two HIV outpatient services of the same city, followed by the same medical staff since mid-2002, very significant differences occur in antiretroviral prescriptions. Given the availability of 18 different anti-HIV drugs, a correct balance of expected long-term efficacy and tolerability rates should be taken into account in relation to every single patient's needs, but also weighted against scheduled costs, to allow the best allocation of future resources in this setting.

PP 4.35.

Comparison of Toxicity and the Dyslipidemic profile of the Two Available non-nucleoside Reverse Transcriptase Inhibitors: significant differences between Nevirapine and Efavirenz

Manfredi R, Calza L, Chiodo F. Infectious Diseases, University of Bologna, S. Orsola Hospital, Bologna, Italy

The abnormalities of serum lipid metabolism occurring during HIV disease treated with combination antiretroviral regimens are usually attributed to protease inhibitors, but similar toxicity could not recover (or may eventually appear) after the switch or the initiation of treatment with a non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). In order to evaluate the toxicity and the serum lipid profile of efavirenz and nevirapine, a cross-sectional survey was performed on a single-centre cohort of around 1,000 HIV-infected patients (p) treated with the relevant antiretrovirals during at least 12 months. When considering patients who were naïve to either efavirenz or nevirapine, 259 consecutive subjects given efavirenz were compared with 236 patients treated with nevirapine, by a multivariate analysis of a large spectrum of potential untoward events, metabolic (dyslipidemic) toxicity, and eventual treatment interruptions. The two compared patient groups proved matched as to demographic and epidemiologic features, HIV disease stage, mean CD4+ lymphocyte count, plasma HIV viremia, HCV-HBV co-infection rate, duration and type of eventual prior antiretroviral therapy, and pre-existing dysmetabolism and/or lipodistrophy (in pre-treated patients). When assessing the 141 antiretroviral-naïve patients, the short-term tolerability rate measured during the first three months did not differ between the two study compounds, but hypersensitivity reactions predominated for nevirapine, compared with central nervous system disturbances for efavirenz ($p<.0001$). Among patients who were already experienced with antiretrovirals, and those on salvage anti-HIV therapy, a grade 1-3 liver toxicity occurred in 19.2% of nevirapine-treated patients, versus a 2.6% rate found in the efavirenz group ($p<.0001$). However, when a non-nucleoside reverse transcriptase inhibitor replaced a protease inhibitor due to prior remarkable lipid dysmetabolism, a drop of triglyceridemia and/or cholesterolemia of at least 30% since the start of efavirenz or nevirapine occurred in 67.4% of patients who switched to nevirapine, versus 28.9% only among individuals who introduced efavirenz ($p<.0001$). Furthermore, dyslipidemia appeared for the first time only after starting a non-nucleoside reverse transcriptase inhibitor in 18.9% of efavirenz-treated patients, versus 2.2% of those given nevirapine ($p<.0001$). The rate of early and late treatment interruption due to toxicity or adverse effects proved similar in the two patient groups. In conclusion, the two available non-nucleoside reverse transcriptase inhibitors seem to have a comparable activity and resistance profile in different clinical situations, but adverse events prove substantially different. The broad spectrum of short- and long-term toxicity, and the very significant differences between the efavirenz and nevirapine profile, are stressed in terms of absolute frequency and mode and time of occurrence. Patients who were pre-treated with other anti-HIV regimens may show a tendency to cumulative liver toxicity for nevirapine, and especially stable or even worsening metabolic and serum lipid abnormalities, in the case of efavirenz. Controlled investigation including the study of pathogenetic mechanisms underlying these profoundly different toxicity profiles of the only two available non-nucleoside reverse transcriptase inhibitors of HIV, is particularly needed.

PP 4.36.

Glycyrrhizin Production from Transformed Licorice Cells

Kovalenko P.G., Maliuta S.S. Institut of Molecular biology and genetics NASU, Zabolotnogo, Kiev, Ukraine

Plant roots are used as a source of pharmaceuticals, dietary products, agrochemical, flavors, fragrances and many others specially chemicals. The limited number of medical plants have been manipulated by genetic engineering and very few pathways of secondary metabolism in them have been understood on molecular level.

However, the roots of licorice have been shown to contain more than 100 other bioactive compounds and especially such as antileukemic inductors [1-4]. Licorice root contains a variety of compounds. The most prominent is the water-soluble triterpenoid glycoside glycyrrhizin (GL). The root content of this compound varies from 2%-4% depending upon growing conditions. GL has been shown in several studies to have antiviral activity against the human immunodeficiency virus (HIV) both in vitro and in vivo. It blocked plaque formation and HIV-specific antigen expression in one in vitro study. In a subsequent study by this same group GL sulfate was found to be four times stronger than GL and was also an effective inhibitor of HIV reverse transcriptase. In addition, several phenolic compounds isolated from licorice, especially licopyranocoumarin, inhibited the cytopathic activity of human HIV in cell culture. Glycyrrhizic Acid (GL) is the major bioactive triterpene glycoside of licorice root (*Glycyrrhiza Radix*) extracts possessing a wide range of pharmacological properties (anti-inflammatory, anti-ulcer, antiallergic, anti-dote, anti-oxidant, anti-tumor, anti-viral etc.). Official sources of GL are *Glycyrrhiza glabra* L. and *G. uralensis* Fish. (Leguminosae). GL is one of the leading natural compounds for clinical trials of chronic active viral hepatitis and HIV infections (preparation Stronger Neo-Minophagen C, SNMC), and its monoammonium salt (glycyram, tussilinar) is used as an anti-inflammatory and anti-allergic remedy. The synthetic transformations of GL on carboxyl and hydroxyl groups were carried out to produce new bioactive derivatives for medicine. GL esters were produced containing fragments of bioactive acids (4- nitrobenzoic, cinnamic, salicylic, acetylsalicylic, nicotinic, isonicotinic). Bioactive amides of GL were synthesized using chloroanhydride technique and N,N'-dicyclohexylcarbodiimide (DCC) method. The synthesis of acylthiourea and -semicarbazones was carried out via the reaction of triacylthiocyanate of penta-O-acetyl-GL with primary amines and hydrazines. The chain of transformations of trichloroanhydride of penta-O-acetyl-GL was made with the introduction of diazoketone groups in the molecule.

Furthermore, as licorice plants can grow only in limited regions in the world. The objective for this purpose it is very important to improve biotechnological potential in *Glycyrrhiza glabra* L., and *G. uralensis* Fischer, in vitro culture.

And the main objective of this work was to examine the hairy roots culture and elicitor-like effect for the increase of the GL production on licorice cells. We report here on the isolation and identification of GL from Ri T-DNA transformed roots of licorice plants species and elicitor's effect, which have been successfully, used for increase the secondary metabolites production. For this purpose, usage of biotechnological and genetic engineering manipulations has been very important to improve quality of important secondary metabolites production.

Materials and methods

Seeds of *Glycyrrhiza* species were obtained from the Crimea Botanical Garden (Ukraine).

Agrobacterium strains LBA/9402 and 8196 were obtained from (INRA, Versailles, France), R1000 (from Prof.H.Kamada, Tsukuba University, Japan).

The bacteria were cultured at 24°C for two days on nutrient agar medium. Four week-old sterile licorice seeds were used as a source of callus and hairy roots culture. Additionally, has been initiated a suspension culture as a source of the suspension protoplasts. These seeds were grown on modified MS (Murashige-Skoog, 1962) medium without growth hormones at 24°C in a light/dark regime of 16/18h were inoculated with each of bacterial strains and incubated in the same conditions. Explants were immersed in Agrobacterium diluted 1:1 (v:v) with liquid MS medium [1:5; 1:10 and 1:20 (v:v)]. Cultures were incubated in the dark. Production of hairy roots was observed on the leaf and petiole explants from cultivated plants when inoculated with *A. rhizogenes* strain 8196 alone or

in combination with acetosyringone. Opine analysis of the cultures transformed by the strain 8196 was performed according the method of (Dessaux Y., et al. 1994). Roots and callus formed on inoculated licorice plants material were used for agropine assay. For this purpose, the samples, weighing from 2 to 4 mg each, were extracted in boiling water for 10 minutes. the samples were centrifuged for 5 minutes and the supernatant removed and taken to dryness under vacuum. The dried supernatant was then brought to a known volume in water and subjected to paper electrophoresis. Spots were visualized by staining with silver nitrate. Samples were compared to a standard consisting of mixture of mannopine, agropine (Sigma Chemical, Co).

Expression of the GUS reporter gene was detected on the explants from in vitro seedlings and inoculated with strains R1000 of *A. tumefaciens* and LBA 9402.

β -glucuronidase activity was determined in extracts using a fluorometric assay or in planta using histochemical staining. For the fluorometric GUS assay in transformed tissue, its were homogenized in 0.5 ml lysis buffer (50 mM Na_2HPO_4 , pH 7.0, 5 mM DTT, 1 mM NaEDTA, 0.1 % sodium lauryl sarcosyl, 0.1 % triton X-100). The homogenate was centrifuged at 12,000 rpm for 10 min in an Eppendorf centrifuge at 5 min and GUS activity of the supernatant was measured as described by Jefferson (1987). For histochemical staining of plant tissues, samples were infiltrated with a staining solution containing 1 mg ml^{-1} X-Gluc (5-bromo-4-chloro-3-indolyl β -glucuronide), 100 mM phosphate buffer, pH 7.0, 5 mM $\text{K}_3[\text{Fe}(\text{CN})_6]$, 5 mM $\text{K}_4[\text{Fe}(\text{CN})_6]$ and 10 mM EDTA and incubated for 6 - 10 h at 37°C. After staining, the plant tissues were fixed in a solution of 5 % formaldehyde, 5 % acetic acid and 20 % ethanol for 10 min at room temperature, and then cleared sequentially in 50 % ethanol for 30 min and 100 % ethanol overnight at room temperature. Stained sections were viewed and photographed.

The amount of 4-methylumbelliferone (4MU) product in transformed tissues after inoculated procedure (h) by LBA 9402 strain, was determined using a fluorescence spectrophotometer (Beckman Instruments, USA), with an λ excitation 365 nm and λ emission 455 nm. β -Glucuronidase activity was normalized to the protein content of extracts determined by the method of Bradford using bovine serum albumin as a standard .

Furthermore, these explants have been produced hairy roots when inoculated with LBA 9402, and 8196 of *A. rhizogenes*. However, the transformed roots via R1000, were slow-growing (0.03-0.07 cm/day) but now branching on the plating medium. The transformed roots were identified as hairy roots. For this purpose, the transformation via 8196 has been confirm as opine analyze.

The measure the growth and secondary metabolite production, the hairy roots were harvested by filtration, washed twice with distilled water, and lyophilized. The ability of the total phenolics production was evaluated by analyzing the total phenolics contents of the transformed cells and the media. The extraction of the soluble phenolics from the lyophilized, powdered tissue was performed by the method of Georgiewsky et al.(1990) [5].

And for this purpose, 30 mg of lyophilized and powdered tissues were suspended in 5 ml of 80% methanol and incubated for 15 min at 70°C. One ml of the methanol extract was combined with 1.8 ml of distilled water and 0.2 ml of Folin-Ciocalteu reagent (Merc Chemical Co). Than, the solution was kept at 24°C. After 5 min, 1 ml of 12 % Na_2CO_3 was added and the reaction mixture was incubated for 2 h at 24°C. Thereafter the absorbance of the solution was measured spectrophotometrically at 739 nm. To determine the total phenolic contents of the media suitable dilution of the samples were used in the Folin-Ciocalteu reaction, and the content of the total phenolics in the roots and the media was calculated according to a standard curve obtained with pyrogallol and expressed as pyrogallol equivalents as mg/l root dry weight or mg/l of liquid medium.

Lyophilized hairy roots were analyzed by TLC chromatography. And for this purpose, the samples were extracted directly with chloroform and samples hydrolyzed with 1 M sulphuric acid before extraction were tentatively analyzed thin-layer-chromatography (Watman silica gel 60A TLC-plates, fluorescent at 254 nm). Ethyl acetate/ethanol/ammonia/water (65:25:1:9) was used as a migration solvent. The TLC -plates was sprayed with anisaldehyde-sulphuric acid solution, and the color and R_f values were compared to reference compounds (glycyrrhetic acid, isoliquiritigenin and liquiritigenin).

Results and discussion

In the present research we have confirmed a method to obtain transgenic licorice roots in which the foreign genes expressed quite efficiently. And the present studies demonstrated that Glycyrrhiza

species is highly sensitive to *Agrobacterium*-mediated transformation, and especially when used a super virulent *Agrobacterium rhizogenes* strains.

Agrobacterium-mediated transformation studies of *Glycyrrhiza* specie have been limited to date. In the present study, three strains of *A. rhizogenes* (LBA9402, 8196) and *A. tumefaciens* R1000(pRiA4/pBI121) and which were used to infect different organs and tissues of *Glycyrrhiza* species in order to evaluate whether *Agrobacterium* could be used for gene transfer in this species. Aerial parts (young leaves and petioles) were inoculated by

From four to eight weeks after inoculating *A.rhizogenes* (LBA 9402 and 8196), numerous adventitious roots appeared at the inoculated sites in the tissue. The axenic root cultures obtained grew with the production of numerous lateral roots on modified hormones free MS medium.

Hairy roots, obtained by transformed of licorice cells with the bacterial soil pathogen *A.rhizogenes*, grow at high rates as compared plant cell suspension cultures. Transformed roots grow rapidly and are highly branched, while normal roots grow very poorly in vitro on modified MS medium and where was contain with 1/5 the normal amount of nitrogen. The infection hairy roots tissues of *Glycyrrhiza* with *Agrobacterium* strains LBA/9402 and 8196 have been identified after 8 weeks on polyphenolic compounds contents according to tentative analyses. The infection rate and the ability of the transformed roots to grow further on a nutrient medium appeared to be highly depended on the *Agrobacterium* strain used. Such as more high levels (3.42 g/l) of the total flavonoids production have been identified on the strains that transformed by LBA 9402 , in comparison with non-transformed control (0.2 g/l).

Agrobacterium-mediated transformation studies of *Glycyrrhiza* specie have been limited to date. In the present study, three strains of *A. rhizogenes* (LBA9402, 8196) and *A. tumefaciens* R1000(pRiA4/pBI121) and which were used to infect different organs and tissues of *Glycyrrhiza* species in order to evaluate whether *Agrobacterium* could be used for gene transfer in this species. Aerial parts (young leaves and petioles) were inoculated by *Agrobacterium* strains. The transformed hairy roots of *G.uralensis* were obtained by infection of *A.rhizogenes* 8196 and with strain as R1000 (Fig.2). either in aseptically grown plantlets. One of the established liquid culture lines produced glycyrrhizin (Fig.1) at a yield of 4.5% dry weight on the period of culture as a 30 days. These metabolites were synthesis from hairy roots on the media with the addition of the some elicitors (Yeast extract, Sigma Chemical Co) in concentration as 500mg/l, and bioextract from fungal mycelia and which has been isolated from *Panax ginseng* endophyte mycorrhizal fungus *Acremonium* sp. This bioextract was prepared for elicitate of the obtained hairy roots.

Concentration of fungal elicitor is indicated by diluted from original bioextract and which originally was prepared on 60% ethanol and than diluted at 10^{-4} to 10^{-6} .

Using this combination (hairy roots and elicitors), were shown the induce of phenolics, including flavonoids and in *G.uralensis* strain was synthesis glycyrrhizin (Table.1 and Table. 2).

The total metabolites production (flavonoids and glycyrrhizin) on hairy roots of *Glycyrrhiza glabra*.

Strains number on modified MS medium	<i>Agrobacterium</i> strains	Elicitors YE (mg/l); fungal extract as diluted	Flavonoids (%; dry weight)	Glycyrrhizin (%;dry weight)
1-MS mod (BA+NAA)	LBA/9402	50-YE+ 10^{-4} f.extr.	10.1	Non-indent.
2-MS (2,4-D+NAA)	LBA/9402	500-YE+ 10^{-6} f.extr.	11.4	Non.ident.
3-MS (2,4-D+BA)	8196	50-YE+ 10^{-6} f.extr.	12.3	Non.ident.
4-MS (BA)	8196	500-YE+ 10^{-6} f.extr	13.8	Non.ident.
5-MS (BA+NAA)	R1000	500-YE+ 10^{-6} f.ext	14.2	Non.ident.

MS-modified Murashige-Skoog (1962) nutrient medium; (BA,NAA,2,4-D-phytohormones).

Table 2

Flavonoids and glycyrrhizin production from hairy roots of *G.uralensis* with the treatment of elicitors.

G. <i>uralensis</i> hairy roots on MS medium #	A. <i>rhizogenes</i> strains	Elicitors (mg/l); fungal extract as diluted	Total flavonoids (% dry weight)	Glycyrrhizin (% dry weight)
1-MS mod (BA+NAA)	LBA/9402	50-YE+10 ⁻⁴ f.extr.	13.4	Non-ident.
2-MS (2.4-D+NAA)	LBA/9402	500-YE+10 ⁻⁶ f.extr.	13.6	Non-ident.
3-MS (2.4-D+BA)	8196	50-YE+10 ⁻⁶ f.extr.	13.9	2.1
4-MS (BA)	8196	500-YE+10 ⁻⁶ f.extr.	14.4	3.6
5-MS (BA+NAA)	R1000	500-YE+10 ⁻⁶ f.ext	14.2	4.5

YE-yeast extract; F.ext.-elicitor, which has been obtained from endophytical fungus *Acremonium* spp., isolated from roots of *Panax ginseng* roots.

Control (non transformed) tissue of *Glycyrrhiza* has contained 3,1-4.2 % per dry weight of the total flavonoids.

Furthermore, the production of phenolic substances per root dry weight was somewhat higher in the medium with elicitors (33 mg per g/l dry weight) resulting a significantly higher volumetric productivity (275 mg/l) compared to that in the original medium (elicitors free) was (118 mg/l). The growth and phenolics production of hairy root clones as LBA/9402 and 8196 were higher to been stable for several subcultures in modified MS medium. The production of phenolic substances (when measured as total phenolics) was considerably high in nutrient medium with elicitors, and according to TLC-analyses the extracts of the cultures contained many different phenolic compounds and among which isoliquiritigenin, liquiritigenin and liquiritin could be detected. Unelicited hairy roots showed a slight decrease in total phenolic content throughout the culture period, while elicitor treated cells reached a maximum concentration of the total flavonoids production from licorice hairy roots. Therefore, we confirmed that combination of yeast extract and fungal elicitors, have stimulated the encrease of GL induction in hairy roots of *G.uralensis* respectively at 7-15 days by the joint of co-culture period with these elicitors. Furthermore, the prolong co-culture period more than 25 days, showed signs of cells necrosis and the decrease of GL production.

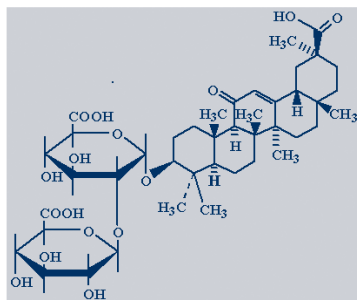


Fig 1. The chemical structure of Glycyrrhizin.

Our results were showed that both combination as hairy roots culture and its elicitors treatment procedure can significantly to increase in 2.5-3 fold time the secondary metabolites production in comparison with control (non-treatment cells).

Conclusions and perspectives

In the present study, we have established a protocol for transfer of a foreign gene into genome of *Glycyrrhiza* plant species using an *Agrobacterium* strains. We have obtained 3 clones which were elicited and which showed on the modified Murashige-Skoog nutrient medium a more high level of the metabolite production (flavonoids and glycyrrhizin) in comparison with control (non transformed cells).

During the last several years, many efforts have been made in the area of genetic manipulation with the secondary metabolism in important medicinal plants.

Transgenic techniques have definitely been offering promising possibilities and indications for future research. However, we need more detail knowledge, in particular, on basic plant biology.

The genetic manipulation of the flavonoid pathways aimed at the change of colors in the callus clusters and in hairy roots. Studies on the concentration of specific phenolic compounds, the variation of these concentrations as a function of environmental factors or root age (as a optimal producing), and comparison between treated and non-treated hairy roots by specific elicitors are under progress.

Quite important the search also functions as the signal (key plant-cell enzyme) that may act in activating later responses, and which can stimulate the accumulation in vitro of metabolites such as flavonoids and terpenes. One of them is phenylalanine ammonia lyase (PAL), which catalyzes the deamination L-phenylalanine to produce trans-cinnamic acid, is a key enzyme at the entrance step from primary (shikimate pathway) to synthesis of flavonoids in plant cells. The approach to study the observed responses in plant tissues and cells lies in experimenter with specific biotic and abiotic elicitors for the stimulating the metabolic pathway.

This way could promote the long-term accumulation of basic knowledge on biochemistry and molecular biology of flavonoid biosynthesis. Quite important will be clarification of cell-type specific secondary metabolite expression with reference to the developmental stage where regulatory genes and promoters are expressed.

For this purpose identification of cis and trans factors that regulate the temporal and spatial gene expression of each secondary metabolite pathway will be very important. The T-DNA genes of Ri (and Ti) plasmids are expressed in the higher plant host cells and, as one might expect, these genes bear the regulatory signals typical of eukaryotic genes. Quite important to investigation of the ability to engineer the genomic DNA of hairy root through tailor made Ri plasmid and will be a break through in producing novel compounds. Using these systems, it may be possible to produce more than one product with a single type of hairy roots.

The results of this experiment shaving a success in transformation of *Glycyrrhiza* species and making relevant the biotechnology possible could be interesting with the purpose of drug discovery and interesting, obtaining new drugs with anti-inflammatory and immunomodulatory effects.



Fig.1. Transgenic licorice" hairy root" culture transformed by strain *Agrobacterium rhizogenes* 8196



Fig.2. Histochemical GUS in transgenic licorice root tissue transformed by strain LBA 9402.

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PP 4.37.
Efficacy of Enfuvirtide in Patients Infected with a Drug-resistant Human Immunodeficiency Virus (HIV-1)

Lebaudy C, Ghnassia C, Poinson Y. Vannes Hospital, France

Enfuvirtide (T-20 or Fuzeon) is the first of a new class of antiretroviral drugs called HIV fusion inhibitors. By binding to HIV glycoprotein 41, it inhibits virus fusion to host CD4+ cells membranes. As Enfuvirtide is a synthetic peptide, it is administered by subcutaneous route. The addition of T-20 to an optimized background regimen leads to a decrease of plasmatic viral load and an increase of CD4+ cell count for patients infected by multidrug-resistant HIV-1.

A 39-year-old man, diagnosed seropositive since april 1990, received previously multiple antiretroviral drugs (bi, tri, quadri and pentatherapy) optimized with the aid of phenotypic and genotypic resistance testing, just as drugs assay. Those therapy were temporary stopped on august 2002 because of their inefficiency (perhaps due to a lack of adherence) and their bad tolerance. Cachexy and major immunosuppression impose an hospitalization and treatment recovery on may 2003. Two months later, enfuvirtide was prescribed at dose 90 mg twice daily as a subcutaneous injection, in association with abacavir-lamivudine-zidovudine (Trizivir) one tablet twice daily, efavirenz (Sustiva) 600 mg once daily and ritonavir-lopinavir (Kaletra) three tablets twice daily. Oral drugs doses were regularly fitted with assay results.

Virologic parameter was defined by the evolution of HIV-I RNA copies per milliliter of plasma. Immunologic improvement was defined by the number of CD4+ cells per microliter of plasma.

	May 03	June 03	July 03	Aug 03	Sept 03	Oct 03
CD4/RNA copies	2/204000	2/NA	2/227000	5/1070	9/260	7/520
	Nov 03	Dec 03	Jan 04	Feb 04	Mar 04	Apr 04
CD4/RNA copies	20/<200	25/<200	25/290	25/290	NA	
65/250						

The main adverse event of enfuvirtide is injection-site reactions (erythema, nodules, moderate pain and discomfort without limitation of usual activities). The benefit of enfuvirtide was demonstrated by significant reduction in the plasma HIV-1 RNA level and the increase in the CD4+ cell count by a relative short time, for this patient who was in therapeutic failure.

PP 4.38. Natural Treatment for HIV/AIDS

Schelonka EP. Good News Medical Clinic, Belize City, Belize, Central America

Clinical investigations have shown that correction of nutritional deficiencies, administration of nutritional supplements and natural therapeutic agents have been effective in delaying the progression of Human Immunodeficiency Virus (HIV) to the Acquired Immunodeficiency Syndrome (AIDS). Vitamin B12 deficiency seen in 10 to 25% of HIV patients indicates rapid progression to AIDS. Patients with the highest Vitamin E levels have the slowest progression to AIDS. Both L-carnitine and Glycyrhizin supplementation cause slowing of the progression of HIV to AIDS. Laboratory studies have identified a large number of natural agents that are superior to synthetic medications in controlling HIV replication. Examples of reverse transcriptase inhibitors are alpha lipoic acid, and Momordica charantia proteins MAP30 and MRK 25. Other natural reverse transcriptase inhibitors are found in the coumarins, flavonoids, tannins, alkaloids, lignans, terpenes, naphthoquinones and anthroquinones. Natural protease inhibitors are bromelain and reishi Mushroom. Curcuma longa is an HIV integrase inhibitor and LTR repeat inhibitor. All of these agents have a favorable side effect profile. When used in combination therapy, L-carnitine is a preventative agent for AZT-related muscle cell dysfunction

PP 4.39.

Vivre avec le Secret du VIH et des Multithérapies pour un Groupe de Femmes Montréalaises

Trottier G, Massie L, Toupin I, Fernet M, Otis J, Pelletier R, Bastien R, Josy Lévy J, Samson J, Boucher M, Lapointe N, Harerimana M et Rateau M. Quebec, Canada

Problématique: Rares sont les travaux de recherche ayant investigué les répercussions du VIH et des multithérapies sur la vie quotidienne de femmes séropositives. La présente étude vise à décrire le vécu de ces femmes aux plans social, familial et relationnel de manière à dégager les enjeux liés à la divulgation du statut infectieux et de la prise quotidienne de traitements antirétroviraux.

Méthodologie: Dans le cadre de cette étude qualitative, les données ont été recueillies auprès de 26 femmes montréalaises, âgées de 25 à 51 ans. Ces femmes, d'origine africaine, caucasienne et haïtienne, ont été recrutées sur une base volontaire, en milieux clinique et communautaire. Le matériel d'entretien extrait de leurs récits de vie a été traité selon la méthode d'analyse de contenu thématique.

Résultats: Les données recueillies montrent que la plupart des femmes interrogées vivent avec le secret de leur statut infectieux et de la prise quotidienne des médicaments. Au plan social, la grande majorité d'entre elles vont exclure de leurs interactions avec parents et amis le fait qu'elles soient séropositives et sous médicaments. Certaines d'entre elles iront jusqu'à hésiter à créer de nouveaux liens d'amitié sous prétexte de devoir, un jour, témoigner de leur statut infectieux. D'autres, habitées par la crainte de rencontrer des personnes connues et de la même origine ethnique, vont se priver d'aide et de ressources, même en sachant que ces dernières vivent aussi avec le VIH. Au plan relationnel, la plupart des femmes célibataires évitent les relations amoureuses ou écartent les partenaires amoureux potentiels. Au plan familial, le désir de protéger ses enfants et de conserver des liens familiaux harmonieux, de même que la peur de voir souffrir les membres de la famille sont les principales raisons du non dévoilement du statut infectieux. À tous les plans, cacher ses médicaments, fuir le regard d'autrui ou invoquer d'autres raisons médicales concernant la prise de médicaments apparaissent comme des stratégies de gestion du secret utilisées par une grande proportion d'entre elles. La peur du jugement d'autrui, l'existence des préjugés, les manifestations de rejet, la discrimination appréhendée et le non respect de la confidentialité constituent les principaux motifs reliés au non dévoilement.

Conclusion : Malgré les bienfaits considérables des traitements antirétroviraux sur l'état de santé des personnes vivant avec le VIH, l'étude montre que la majorité des femmes vivent beaucoup d'isolement aux plans affectif et social engendré par la peur reliée au dévoilement. Afin de mieux outiller les femmes sur les conditions facilitant la révélation de leur statut infectieux, il importe d'informer ces personnes et les intervenants de la santé et des services sociaux sur les motifs, contextes et conséquences qu'entraîne le fait de divulguer ou non un secret.

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PP 4.40. Two-drug ART in Treatment Naïve HIV-infected Persons in Resource-limited Setting: 2-year study

Yanamadala VMKR. Association of People Against AIDS, Kakinada, Andhra Pradesh, India

Background: In developing and poor countries all the HIV infected persons are anti-retroviral therapy(ART) naïve and the number of ARVs available is limited. Only a limited number of patients can afford ART and even among them, majority can afford two-drug combination only. The effectiveness of a 2-drug ART is followed-up for 2 years.

Methods: 220 HIV infected symptomatic and asymptomatic adult patients attending as out-patients at our AIDS speciality clinic with CD4 counts ranging from 96 to 520 are given either ZDV/3TC or d4T/3TC. Critically-ill patients, who need hospitalization are excluded from the study. The importance of adherence and continuous treatment was explained. The treatment efficacy assessed by clinical and Immunological parameters.

Results: Out of the 165 patients followed for CD4 counts every six months, 152 patients showed consistent improvement in CD4 counts and general health. 13 patients showed a decline at one point during this course, and soon after the patients were identified with various illnesses, viz., viral fevers, appendicitis etc... Their CD4 counts were also improved in the subsequent test after 6 months. Increase in CD4 count ranged from 172 to 305, with a mean increase of 245 cells at the end of 2 years.

Conclusions: Dual ART among treatment naïve HIV infected persons is an effective and enduring option in resource-limited settings and leaves future options open. Improvement in overall health is sustained after 2 years. With generics, two drug ART combination available at a minimum cost of 30 USD per month, dual ART may be advocated in developing and poor countries after large-scale studies.

PP 4.41.

The Dissociation Between Immunologic and Virologic Response to HAART

Pesic I, Salemovic D, Ranin J, Zerjav S, Jevtovic Dj. The Institute of Infectious and Tropical Diseases, Belgrade, Serbia & Montenegro

Objective: The introduction of highly active antiretroviral therapy has resulted in maximal control of viral replication and restoration in immune system functions among patients with HIV-induced immunodeficiency. However, a significant proportion of patients cannot achieve immune reconstitution, even though their viral load reached undetectable. The aim of this study was, by using an electronic database, to determine risk factors that are associated with the dissociation between optimal virologic and sub optimal immunologic response to HAART

Methods: Using the electronic data base the cohort of 380 HAART-treated patients who have been regularly followed-up in the HIV/AIDS Department of Infectious Diseases University Hospital in Belgrade were analysed for the prevalence of the virologic-immunologic dissociation in response to HAART **Results:** Out of 380 pts on HAART 73% reached the optimal virologic response meaning less than 50 copies of HIV RNA/ml of plasma after mean time of 32.91: 24 months. Of those, 22% did not manage to raise their CD4 cell count over 400/mm³. In this subpopulation of patients mean CD4 cell count was 172±100/mm³. According to the Cox regression model the factors most predictable for immunologic failure despite achieving an undetectable viral load, were pre-treatment CD4 cell count below 100/mm³ (OR 3.0, 95%CI 1.6-6.9), usage of protocols with 3 NRTIs (OR 3.2, 95%CI 1.4-6.4), while usage of 2 NRTIs +PI was a negative predictor for the dissociation (OR 0.2, 95% CI 0.1-0.5). Patient's age of over 40 was not a significant predictor. **Conclusion:** According to our data deeply immunosuppressed HIV infected patients are less likely going to achieve the immune restoration while on HAART, and/or if treated with protocols without PIs. In other words, protocols comprising of 3 NRTIs seems to be less potent in more advanced patients.

PP 4.42. Utilization of HIV Post Exposure Prophylaxis Among Health Care Workers in Selected Health Institutions In Nairobi

Maina JW, Wasunna MK, Orago AS, Okelo RO. Kenyatta University, Nairobi, Kenya

Introduction:

Although avoiding contact with infected blood is one of the primary strategies of preventing occupationally acquired Human Immunodeficiency Virus (HIV) infection, appropriate post-exposure management (PEP) is an important element in workplace safety. The concern to optimise such interventions is heightened if the institution caters for populations in which the prevalence of HIV is high, as is the case of health facilities in Nairobi Province, Kenya. In their practice the exposure of Health Care Workers (HCWs) to blood and other potentially infectious body fluids is of major concern and justifies a specific prevention and surveillance strategy.

Method:

This was a descriptive cross-sectional study that sought to establish the main factors that underlie utilization of PEP services among the occupationally exposed Health Care Workers in Nairobi Province, Kenya. The instruments used for data collection included a questionnaire for HCWs in direct care of patients, a question guide for focus group discussions (FGDs). A total of 179 purposively sampled health-care workers consisting of nurses, physicians, surgeons, dentists and laboratory personnel were interviewed. Three focus group discussions were carried out among HCWs in the three hospitals namely Kenyatta National Hospital, Aga Khan Hospital and Mbagathi District Hospital.

Results and Discussion:

Knowledge of risk of occupational HIV transmission and available options for PEP was below average with only 54.8% having adequate knowledge. Although the majority (92.2%) of the respondents strongly believed that they were at risk of contracting HIV/AIDS from occupational exposure and 83.2% of these had taken a protective measure against occupational exposure to HIV, they did not know the options available for PEP. However, they also correctly identified other blood borne diseases that pose a risk to the HCWs at the work place such as HBV, HCV and HTLV I and II.

Almost half (45.8%) of the respondents had rational attitude towards PEP. However, they had the misconception that adverse effects caused by antiretroviral regimens used were irreversible. Only 14.7% of the previously exposed respondents reported that they had utilised PEP services that is, had sought professional attention. There was need to increase awareness of occupational HIV transmission and the available options for PEP so that a more rational attitude towards PEP is developed. Improving HCW education, information and communication would bridge the knowledge-practice gap and achieve this.

Conclusion:

An urgent need for the government to formulate and enforce through appropriate strategies, a policy on HIV-PEP for public health institutions has become evident. This calls for a multidisciplinary expert consultation to put together feasible suggestions and assess the most appropriate implementation process.

PP 4.43.

High Thymic Volume and Output at Baseline is Associated to Enhancement of Viral Replication and Immunologic Impairment Early after HAART Discontinuation in Chronic HIV Infection

Vallejo A, Valladares A, De Felipe F, Vivancos J, Soriano-Sarabia N, Gutierrez S, Molina-Pinelo S, Ruiz-Mateos E, Lissen E, Leal M. Hospital Virgen del Rocio, Seville, Spain

Objective: To analyse viral and immune dynamics after treatment interruption and to determine whether thymic-function related markers play a role in preventing CD4 count decline caused by increased viral replication.

Design and methods: HAART was discontinued in an open cohort of 46 patients with a mean 1000 CD4 cell count and prolonged viral suppression. They were followed every 4 weeks until this study was censored after 24 weeks. Re-initiation of treatment was driven by CD4 cell count regardless HIV RNA level. Thymic volume, TREC level, and naïve and memory T cells were analysed at baseline and after 12 weeks.

Results: At baseline, patients with bigger thymic volume and higher naïve CD4 cell count achieved both a higher plasma viral load in a shorter period of time, as well as a significant greater decline of CD4 cell count. On the other hand, naïve and memory CD4 count, as well as TREC level declined significantly after 12 weeks of discontinuation. Based on viral replication rebound during the follow up, three different patterns were observed: patients with a high and rapid viral replication (RH); patients with delayed high viral replication (MH); and patients with lower viral replication during the follow up (LS). RH pattern correlated with higher CD4 count decline and higher thymic volume at baseline.

Conclusions: During treatment interruption viral load rise occurred following three different patterns, and TREC and naïve T cells decreased probably involving a decreased thymic output. Surprisingly, bigger thymic volume and high naïve CD4 counts, significantly found in RH pattern, not only did not prevent immune and virologic impairment but, on the contrary, enhanced it probably due to infection of increased number of available target cells. Since long term consequences of these observations are unknown, treatment interruption has to be taken with caution by clinicians.

PP 4.44.**The Benefit of the Combination Antiretroviral therapy (ART) for the Treatment of HIV infected Patients in Slovakia**

Habekova M, Stanekova D, Mokrá M. Slovak Health University -Institute of Preventive and Clinical Medicine, Department of Geographical and Infectious Medicine of Dérer Hospital, Bratislava, Slovakia

Introduction:

The benefit of the combination antiretroviral therapy (ART) for the treatment of infection with HIV-1 produced sustained reductions in plasma HIV-1 RNA to levels below the limits of detection and resulted in reductions in disease progression. Many factors that should activate the disease progression and can contribute to treatment failure.

Patients and methods:

39 patients of the group of 51 HIV infected patients observed have been treated with ART composed from 2 NRTi (usually AZT plus 1NRTi), or from 2NRTi plus 1nNRTI. Disease stage, CD4+ lymphocyte count, and plasma HIV-1 RNA level were examined as the predictors of response.

Results:

Approximately 80% of treated patients had a treatment response (viral load change - 0,5log), 20% of patients failed to respond to used regimen. The results of observation of our group of patients have shown the clinical benefit of the treatment.

Discussion:

The factors as the emergence of drug resistance and pharmacodynamics should play an important role in limiting the long-term success of ART and could be monitored prior and during the therapy.

PP 4.45.

Virologic efficacy and pharmacokinetic of Saquinavir/Ritonavir baby dose once daily (QD) combination in PI (protease inhibitor) pretreated HIV-1 + patients

F Brunel-Dalmas(1), JM Livrozet(1), MC Gagnieu(1), JP Bru(2), C Michon(2), JL Touraine(1)

(1) Hôpital E. Herriot, Lyon (2) Hôpital d'Annecy. With the collaboration of Roche France

Objectives: To study virologic efficacy, compliance and pharmacokinetic of an antiretroviral therapy included QD saquinavir (SQV) + ritonavir baby dose (r) combination (1600mg-100 mg x1/d).

Methods: 11 HIV+ SQV naïve patients in virologic failure with a first PI regimen were included in a 12 months prospective study in order to determine virologic efficacy of QD saquinavir soft-gel capsule/r combination (1600mg-100 mg x1/d) associated with 2 Nucleosid Reverse Transcriptase Inhibitors (determined by genotypic test). Clinical, viro-immunological and SQV and ritonavir (RTV) pharmacokinetic exams were performed at baseline, M1, M2, M3 and then every 3 months. Trough and post-dose (3h30 post treatment) plasma concentrations (C_{min} and C_{max}) were determined. Patient Medication Adherence Questionnaire (PMA Q7) was used to evaluate compliance at each visit.

Results: Six patients were evaluated for viro-immunology and pharmacokinetic. At S48, all patients obtained a sustained plasmatic viral load (VL) lower than 20 copies/ml (even when baseline VL was > 5 log).

SQV/r QD combination compliance was excellent (range from 80% to 100%).

For all 6 patients: trough plasma concentrations of SQV were above 0.04 mg/l (cut-off for this study) at all times of measurement. RTV C_{max} concentrations confirm the booster effect of a low dose of RTV combined with SQV in QD regimen.

No significant difference was observed between the first and others months in SQV and RTV trough plasma concentrations (p=0.31 and p=0.61 respectively).

Principal side effects were diarrhea and post treatment nausea in the morning

Conclusions : Our study suggests that in HIV + patients in virologic failure with a first line of PI therapy, the combination of 1600 mg of Saquinavir and 100 mg of Ritonavir in a QD dosing regimen is effective with a virologic efficacy, probably due to therapeutic trough plasma concentrations.

PP 4.46.**Early HCV-RNA Kinetic In HIV Patients With Chronic Hepatitis C Treated With PEG-IFN Alpha-2a And Ribavirin**

Setti M, Bianchi S, Basso M, Sticchi C, Pelli N, Murdaca G, Indiveri F, Picciotto A. Department of Internal Medicine, Department of Health Sciences, University of Genoa, Genoa, Italy

Aim: To evaluate the early response to anti-HCV therapy with Pegylated Interferon a-2a (PEG-IFN a-2a) plus ribavirin, and the impact of the treatment on the immune and HIV virological statuses.

Methods: Ten patients, (8 male and 2 female, median age 40, range 38-42 years) received therapy with PEG-IFN alpha-2a (180 mcg weekly subcutaneously) and ribavirin (800-1000 mg/daily according to body weight), for six months in the HCV genotype 3 (4 patients) and for 12 months in the HCV genotype 1 or 4 (6 patients). Combined antiretroviral therapy was concomitantly given in all but 2 patients. Pre-treatment liver biopsy showed chronic hepatitis in 6 patients and cirrhosis in 4 patients. CD4 cell count was greater than 250 cells/microliter. Clinical evaluation, laboratory tests, qualitative PCR for HCV RNA, CD4 cell counts and determination of plasma HIV RNA levels, were performed at days 7, 14, 28 and monthly thereafter up to 6 months. The median baseline level of HCV RNA was $1,4 \times 10^6$ UI/ml (range $1,13 \times 10^5$ - $3,89 \times 10^6$). The median ALT value at baseline was 159U/L (range 45-299). All patients but 3 had undetectable plasma HIV at baseline control.

Results: We report on the preliminary results obtained in 7 patients at month 6 and in 3 at month 5. Negative serum HCV-RNA values were recorded in 2 patients at day 14 and in 7 at day 28, in 6 at month 3 of treatment. In one patient with genotype 4 HCV became redetectable at month 3. In 6 patients HCV-RNA was still negative at month 6. Three remained viraemic for HCV. No significant changes in most non-target sensitive laboratory parameters were observed. No variation in patients' HIV viral load was found from baseline, whereas a decrease in CD4+ cell count was seen in all patients, though never > 50% nor below 200 cells/microliter. ALT levels normalized in 3 patients (2 at day 28 and 1 at month 3). No severe hepatotoxicity was observed compared with the baseline transaminases and bilirubin, according to the modified criteria of the AIDS Clinical Trial Group. Platelets fell below 50.000 in one patient, requiring a decrease in the dose of IFN to 90 mcg. Clinical adverse events (fatigue, mild depression, insomnia and weight loss) were observed in 3 patients, at month 3.

Conclusions: PEG-IFN alpha-2a plus ribavirin is a well tolerated, feasible therapy in patients with HIV-HCV co-infection: if our preliminary observation of a very early viral serum clearance (= 1 month) is confirmed on a larger number of cases, that parameter might be used as an early indicator for targeting treatment to responders.

PP 4.47.

Nanoparticles associated to zidovudine as an innovative approach for targeting intestinal reservoir during HIV infection

Dembri A, Soursac M, Thomas CM, Maquin A, Cheret A, Ponchel PG, Constantini D. Bioalliance pharma, Paris, Laboratoire de Pharmacie Galénique, Université Paris XI, Châtenay-Malabry, France

Purpose: Therapeutic strategies aimed at eradicating HIV need to be active in mucosal lymphoid tissues acting as virus reservoirs and major replication sites. The gastrointestinal tract (GI) as such, is the largest lymphoid organ and has been shown to be a persistent viral reservoir. For the clinical management of infected patients, zidovudine (ZDV) remains one of the most prescribed antiretroviral. Since this reverse transcriptase inhibitor has no particular affinity for the mucosa, our aim, using nanoparticles technology, was to target the GI and concentrate this drug within this reservoir.

Methods: Transdrug™ (poly(isohexyl) cyanoacrylate) nanoparticles have demonstrated bio-adhesive properties allowing their prolonged localization in the GI tract after oral administration. ZDV associated to Transdrug™ have been synthesized. In vitro anti retroviral effect of this formulation was tested on HeLa P4 cell line infected with HIV-1 Bru strain. After gastric intubations of rats, distribution of ZDV component of the new formulation along the intestine and within organs was compared to a ZDV solution (80mg/kg) at several time intervals. Pharmacokinetics studies were performed in parallel.

Results: In ZDV-Transdrug™ formulation 60% of ZDV is trapped in nanoparticles and 40 % is free. We first confirmed that in vitro ZDV-Transdrug™ antiviral efficacy was similar to the ZDV solution's one. Secondly we demonstrated that ZDV-Transdrug™ ensured higher ZDV concentrations in the GI mucosa compared to the solution. After oral administration to rats, intestinal concentrations of ZDV was up to four times higher using ZDV-Transdrug™ compared to the solution. After 2 hours, ZDV concentration for nanoparticles was 369 µg per gram of tissue vs 80 µg/g and 277 µg/g for nanoparticles vs 37 µg/g after four hours. AUC of ZDV brought by Transdrug™ technology remained 50% lower than the solution. This proportion corresponds to free ZDV fraction and supports the intestine as the main target of ZDV nanoparticles.

Conclusion: Using rat model, ZDV-Transdrug™ have demonstrated in vivo abilities to interact with the digestive membrane, thus creating an increased local ZDV concentration. Nanoparticles represent a promising carrier to specifically target GI reservoir during HIV-1 infection. Future studies will focus on the demonstration of in vivo efficacy.

PP 4.48.**Higher Risk of Antimalarial Treatment Failure in HIV Positive than in HIV Negative Individuals with Clinical Malaria**

Van geertruyden JP, Mwananyanda L, Chalwe V, Mwanakasale V, Moerman F, Chilengi R, Kestens L, D'Alessandro U. Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium; Tropical Diseases Research Centre, Ndola, Zambia

HIV infected pregnant women have a higher prevalence of peripheral parasitaemia and placental malaria and the risk of clinical malaria is significantly higher in HIV+ adults, increasing with falling CD4+-T cell counts. Considering that antimalarial drug efficacy is the result of the interaction between the drug activity and the immune system, it is unknown whether HIV-infected individuals with clinical malaria respond as well to treatment as HIV negative patients. A randomised controlled trial to examine the safety and efficacy of artemether-lumefantrine (AL) and sulfadoxine-pyrimethamine (SP) in adults with uncomplicated *P. falciparum* malaria in Ndola, Zambia, is ongoing. The interim analysis shows an efficacy at day 45 after treatment of 84% for AL and 75% for SP. However, after stratification by HIV status, the efficacy of AL was of 88% in HIV negative, 75% for HIV positive with 300 CD4/ μ l or less, 100% for HIV positive with over 300 CD4/ μ l ($p=0.029$). Similarly SP efficacy was 78%, 52%, 82% ($p=0.017$) in the 3 groups of patients. Interestingly, HIV infected individuals with CD4 above 300/ μ l tend to respond better to antimalarial treatment than HIV negative patients. However, patients with a CD4 count of 300/ μ l or less seem at higher risk of treatment failure. At time of enrolment, the proportion of patients with CD4 under 300/ μ l was higher then expected (59% of the HIV infected), indicating that a large proportion of HIV+ individuals with malaria might fail adequate antimalarial treatment.

PP 4.49.

Inhibitor Design for Drug-Resistant Forms of Aspartic Protease of HIV

Frečer V., Miertus S. International Centre for Science and High Technology, UNIDO, AREA Science Park, Trieste, Italy

Aspartic protease (PR) of HIV cleaves viral polyprotein precursors and plays a key role in the maturation of HIV particles and virus replication. HIV PR has become the target of antiretroviral agents. A number of substrate or transition-state-mimetic pseudopeptide inhibitors has reached the stage of clinical trials and several have been approved for anti-HIV therapy. The PR inhibitors cause significant initial lowering of the viral load in tissues of patients although viral resistance to the inhibitory effect of these drugs develops rapidly. Therefore, there is a constant need to design new anti-HIV agents as well as new strategies to overcome the drug-resistance and cross-resistance problems.

We report here a molecular design, synthesis and enzyme inhibition study of small and flexible C2-pseudosymmetric peptidomimetic inhibitors of HIV PR that contain hydroxyethylene and dihydroxyethylene transition-state-isostere cores. A QSAR model was developed for a training set of fourteen diverse potent HIV PR inhibitors with published crystal structures using a molecular modelling approach. Enzyme-inhibitor complexation Gibbs free energies computed via molecular mechanics and molecular dynamics methods were correlated to the observed enzyme inhibition constants resulting in a QSAR model capable of predicting inhibitory potencies for new HIV PR inhibitors. A series of peptidomimetic inhibitors of HIV was then designed with binding driven also by PR backbone interactions and by hydrophobic forces, which enhance the potential use of these inhibitors against mutant drug-resistant PR forms. Several inhibitors were predicted to bind HIV PR stronger than the reference inhibitor Ritonavir. The most promising compounds were synthesised with two stereoisomers of the central core and were assayed for the HIV PR inhibition. The most potent synthesised inhibitors displayed IC₅₀s of 3 - 5 nM against the wild type HIV PR comparable to that of Ritonavir.

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PP 4.50.**Efficacy of enfuvirtide (FUZEON®) in HIV1-infected patients with failure or intolerance to antiretroviral treatment**

Faye F, Darque A, Ravaux I, Gallais H, Gensollen S, Timon-David P, Bongrand MC. Pharmacy, Public Hospital System Conception, , Infectious diseases ward, Marseille, France

Introduction : Retrospective study from August 2001 to March 2004. Immunologic and virologic follow-up over a 30-month period.

Methods : Patients were 31 males and 6 females divided in two groups according to treatment failure status. Group 1 (n=18) included patients with failure or intolerance to NRTI, NNRTI, and IP. Group 2 (n=19) included patients with failure or intolerance to 1 drug of each above antiretroviral class. Median age was 44 years (33; 62).

Results : For patients of group 1, median HIV-1 RNA levels were 263953 (4890; 1900000), 20275 (<400; 727000), 79300 (<400; 1960000), 1101000 (462000; 1740000), 376350 (17700; 735000), 88302 (11500; 445000), 550000 (261000; 1000000), copies/ml at baseline, M3, M6, M12, M18, M24, M30, respectively. Viral load decrease from baseline was 1.2, 0.5, 0.4, 0.6 log₁₀ (p>0.05), for M3, M6, M18, and M24, respectively. Viral load increase was 0.5 and 0.3 log₁₀ (p>0.05), for M12 and M30, respectively. Median CD4 count was 77 (2; 423), 86 (7; 227), 107 (7; 306), 37 (2; 269), 12 (3; 344), 347 (4; 558), 14 (1; 321) cells/mm³ at baseline, M3, M6, M12, M18, M24, M30, respectively (p>0.05).

For patients of group 2, median HIV-1 RNA levels were 94450 (437; 3510000), 489 (<400; 1050000), 572 (<400; 1620000), <400 (<400; 42500), 1770 (<400; 479000), <400 (<400; 565), <400 (<400; <400), copies/ml at baseline, M1, M2, M3, M4, M5, M6, respectively. Viral load decrease from baseline was 2.3, 2.3, 2.4, 1.7, 2.0, 2.4 log₁₀ (p<0.05), for M1, M2, M3, M4, M5, M6, respectively. Median CD4 count was 84 (4; 360), 150 (10; 400), 100 (10; 335), 117 (50; 232), 153 (59; 338), 156 (56; 212), 119 (119; 119) cells/mm³ at baseline, M1, M2, M3, M4, M5, M6, respectively (p<0.05). Mean weight was 66+/-8 and 66+/-11 kg for group 1 and 2, respectively. There was no significant weight gain from baseline.

Discussion : Enfuvirtide had immunologic and virologic efficacy in patients with failure or intolerance to antiretroviral drug, particularly in those with remaining treatment options. Patients reported increased quality of life. This item was a major asset for the patients during this study and is to be further evaluated.

PP 4.51.

PC-815, a Novel Combination Microbicide

Romero JF, Thorn M, Phillips D. Population Council, New York, USA

The following is a report on PC-815, a novel microbicide that combines the microbicide Carraguard™ and the non-nucleoside reverse transcriptase inhibitor (NNRTI) MIV-150 (Medivir AB). Pre-clinical studies indicate that Carraguard is effective in preventing HIV, SIV, HPV, HSV, and *Neisseria gonorrhoea* infection in vitro or in animals, and clinical trials show that the formulation is stable, safe, and acceptable in humans. Studies done by Medivir show that MIV-150 is highly efficacious in blocking infection by many HIV strains including strains resistant to other RT inhibitors. Animal studies show that MIV-150 is non-toxic, and clinical trials demonstrate that the compound is well tolerated and not easily systemically absorbed. We present evidence that MIV-150 in Carraguard can neutralize free virus. Strong evidence suggests that PC-815 is more efficacious in blocking infection in lymphoma cells than Carraguard or MIV-150 alone. PC-815 also prevents infection of all clinical isolates of HIV tested in PBMCs. In most cases, PC-815 is an order of magnitude more efficacious than Carraguard. By testing efficacy against HIV in vitro, using HPLC, and measuring the viscosity of the formulation, PC-815 was found to be stable for 3 months at 40°C. PC-815 is, therefore, a promising safe, stable and, efficacious microbicide.

PP 4.52.**Lack of an effect of Atazanavir on Steady-State Pharmacokinetics of Methadone in Chronically Treated Subjects**

Friedland G, Andrews L, Agarwala S, Schreiber T, Daley L, Child M, Wang Y, O'Mara E. Yale School of Medicine, New Haven, CT; Bristol-Myers Squibb, Princeton, NJ, USA

Background: Antiretroviral treatment (ART) of opiate addicted drug users with HIV disease often requires management of substance abuse, most commonly with methadone. Pharmacologic interactions between ARTs and methadone are well known and may result in opiate withdrawal or increased side effects, adversely affecting medication adherence and therapeutic success. Atazanavir (ATV) is a potent, safe and effective once-daily (QD) azapeptide protease inhibitor and a moderate inhibitor of CYP3A4. The objective of this study was to examine the possibility of a pharmacologic interaction with ATV and methadone in subjects chronically maintained on methadone. **Methods:** A multiple dose, open-label, sequential, non-randomized study was conducted in 18 HIV-negative subjects stabilized on a given dose of methadone for at least three weeks. Methadone pharmacokinetics (PK) was assessed over a 24-hour period on Study Day 1, ATV (400mg) and methadone were co-administered for 14 days and PK of both were assessed on Study Day 15. Steady-state PK for dose normalized total methadone, R (active) and S (inactive) isomers of methadone and ATV were derived from plasma concentration versus time data. Adverse events, including opiate withdrawal and excess were monitored daily by standardized measures. **Results:** On co-administration with ATV, exposures to the active isomer, R-methadone (AUC 3% and C_{min} 11% greater, respectively, and C_{max} 9% lower) and total methadone (AUC and C_{max} decreased by 6 and 15% respectively, C_{min} increased by 2%) were not significantly affected compared to methadone alone. The AUC, C_{max} and C_{min} of the inactive isomer, S-methadone was lower by 15, 21 and 10%, respectively. Clinically relevant symptoms of opiate withdrawal or excess were not detected. Exposures to ATV were generally comparable to previously reported values. **Conclusions:** Exposures to the active R-isomer and total methadone were not significantly affected by co-administration with ATV. Compared to historical controls, exposures to ATV did not appear to be affected by methadone, therefore indicating lack of a significant PK interaction between ATV and methadone. Dosage adjustment is not recommended when ATV is co-administered with methadone.

PP 4.53.
Follow Up of the Resistance Mutations Archives During Genotype Guided HAART

Parisi SG, Mazzi R, Gatti F, Carolo G, Nicastrì E, Concia E, Dal Bello F, Montano M, Palù G, Andreoni M. Microbiology Dept, Padua Hospital, Padua, Public Health Dept, Tor Vergata University, Rome, Infectious Diseases Dept, Verona Hospital Verona, Italy

INTRODUCTION: to evaluate the kinetic of disappearance of resistance mutations in PBMCs of patients from plasma genotype guided HAART (GART) and during a follow-up period of a successful therapy.

METHODS: drug-resistant mutations in PBMCs of 10 patients at GART and during a mean of 23 months of follow up (median 19 months, range 16-34) were evaluated. Plasma viremia was always undetectable during follow up.

RESULTS: At GART, patients had a baseline mean of 319 CD4/?l, and plasma RNA of 28,216 copies/ml. 7/10 patients had taken >2 PI, 7/10 >4 NRTI and 9/10 one NNRTI. Mean number of baseline mutations was 1,2 primary and 2,5 secondary for PI and 3,2 and 2,8 for RT. At 20 months follow up CD4 were 496 and RNA <50; despite always undetectable plasma levels in all patients, five subjects showed no difference in archived pattern, two patients acquired 77I in PR or 215Y in RT, and three patients lost 1 (103N) or 2 (188L/215Y or 103N/210W) mutations in RT. At evaluation of three patients after 34° months of follow up and with undetectable plasma viremia, one had genotype pattern still unmodified, another acquired 41L/181C in RT and another acquired only secondary mutations. Two subjects simplified therapy after 22 months: one patient reintroduced 2

	ATV/RTV N=119	LPV/RTV N=118	ATV/SQV N=110
Grade 2-4 related AEs (in 15% of patients)	% of Patients		
Total	29	25	26
Diarrhea	3	11¶	6
Jaundice	6	0	2
Nausea	3	2	8
Vomiting	0	<1	4
Scleral icterus	3	0	0
Grade 3-4 laboratory abnormalities	% of Patients		
Total bilirubin	49	<1	20
ALT/SGPT	4	3	4
AST/SGOT	3	3	2
Lipids	Mean % change, baseline to Week 48*		
Total cholesterol	-8	+6†	-4
HDL cholesterol	-7	+2	+4
Fasting LDL cholesterol	-10	+1	-3
Fasting triglycendes	-4	+30†	-14
Concomitant medications	% of Patients		
Antidiarrheal	6	24‡§	13
Lipid lowering	8	19¶	12

previously used drugs, and failed within 3 weeks; the other maintains RNA <50 cp after 13 months of the new therapy. Drug resistant primary mutations for 2 and 1 drugs included in simplification therapy were retrospectively detected in two patients' PBMCs.

DISCUSSION: After 16-34 months, despite HIV-RNA <50 cp in all patients, the absence of blips verified every 2 months and a consistent CD4 recovery/redistribution, the genotypic pattern of a previous failing HAART was still detected in PBMCs in all patients. During a successful GART, the long term persistence of the complete pattern of mutations archived in PBMCs urges to evaluate correctly and with caution another switch or the reintroduction of previously used drugs, particularly in a simplification therapy encouraged by a long term virologic success.

PP 4.54.**Long Term Immunological Benefit with Double Nucleoside Therapy : Genotype Markers**

Parisi SG, Mazzi R, Sarmati L, Gatti F, Carolo G, Concia E, Montano M, Dal Bello F, Palù G, Andreoni M. Microbiology Dept, Padua Hospital, Padua, Public Health Dept, Tor Vergata University, Rome, Infectious Diseases Dept, Verona Hospital Verona, Italy

INTRODUCTION: double antiretroviral therapy (DART) is still used by HIV-infected patients who started treatment many years ago, with a steady and satisfactory viro-immunological situation, and don't accept HAART side effects. We studied virological and clinical correlates of long term DART.

METHODS: 21 HIV-patients (9 male, 12 female) always treated with DART with 2 nucleoside analogues were studied. Demographic, virological and immunological parameters were analyzed at different follow up until a mean of 70 months (mo) of DART.

RESULTS: After a median of 72 mo (range 44-108 mo), CD4 grew from a median of 322/ul (range 105-518) to 392 (median, range 168-1072), HIV-RNA from 14430 cps/ml (median, range 689-137374) fell to 1409 cps (median, range 98-5887). During the entire follow up period in most patients HIV-RNA was detectable >50 cps and in all was stable <6000 cps. 18 out of 21 patients were treated with lamivudine and 184V mutation was detected at last time point in all of them. In 7/7 subjects another sequence was previously obtained after 24-36 mo of DART, and 184V was already detectable. The mean number of primary mutations at last follow up was 1.6, and was related to therapy (zidovudine, stavudine, lamivudine, didanosine). No mutations were found in a patient treated with zidovudine/didanosine after 72 mo, despite a marked increase of CD4 and persistent detectable low level HIV-RNA, stable until 96 mo of observation; neither mutations were found in plasma and PBMC of this patient 35 mo earlier. Another subject showed a stable pattern at 84 and 102 mo of DART, with 497 HIV-RNA cps. On PR, 63P was found in 11/21, and 77I in 8/21 patients.

DISCUSSION: Standard guidelines of antiretroviral therapy on adults recommend the switch from a DART to a fully suppressive regimen. Nevertheless a few patients still experience long term immunological benefit despite persistent low level viraemia during DART. In these subjects genotype analysis show a persistent detection of low number of RT primary mutations and a presence of HIV strains with low level replication competence.

PP 4.55.

HIV-1 Drug Resistance Among Tunisian Subjects With Therapeutic Failure

Jlizi A, Ben Halima M, Slim A, Tebourski F, El Gaaied A, Ben Chaabane T, Chakroun M, Letaief-Ommezinz A, Garbouj M. Laboratoire de Microbiologie, Hôpital Charles Nicolle, Laboratoire de Génétique Moléculaire, Immunologie et Biotechnologie, Faculté des Sciences, Service de Pathologie Infectieuse, Hôpital La Rabta, DSSB, Ministère de la Santé Publique, Tunis, Service de Pathologie Infectieuse, Hôpital Fattouma Bourguiba, Monastir, Service de Pathologie Infectieuse, Hôpital Farhat Hached, Sousse, Tunisia

Introduction: The selection of resistant HIV-1 mutants under treatment pressure, is the main cause of treatment failure. The aim of this study was to characterise resistance mutations in reverse transcriptase (RT) and protease genes, to analyse the effect of these mutations on susceptibility to antiretroviral (ARV) drugs

Methods: Plasma samples of 40 patients failing ARV therapy were tested for genotypic resistance to Nucleoside RT Inhibitors (NRTIs), Non Nucleoside RT Inhibitors (NNRTI) and Protease inhibitors (PI). Resistance mutations were examined using two distinct line probe assays, LiPA HIV-1 RT and LiPA HIV-1 Protease assays. These tests determine the presence of wild-type and or mutant genotypes at codons 41, 69, 70, 74, 75, 184, 215, 151, 103, 106, et 181 of RT gene and at codons 30, 46, 48, 50, 54, 82, 84 and 90 of protease gene. For each drug, Viruses susceptibility was interpreted according to the ANRS-AC 11 algorithm.

Results: Seventy-five percent of the individuals were males, 70% were aged between 20 and 40. Median CD4 cell count and HIV RNA log viral load were 113.5 cells/mm³ and 4.72 copies/ml respectively. The subjects had previous exposure to AZT (70%), 3TC (92.5%), DDI (40%), D4T (25%), IND (82%) and EFV (42%). The median treatment duration was 18.5 months.

The most common NRTI resistance mutations were 184V (60%), 215Y (25%) followed by 41L (12.5%), 70R (10%), 69D/74V (5%) and 151M (20.5%). The 103N mutation was the predominant NNRTI resistance mutation (32.5%) and the main PI resistance mutations were 82A/F (22.5%), 90M (17.5%) and 46I (15%).

The mutation interpretation shows that 88% of viral variants were resistant to one or more drugs (72% to NRTIs, 35% to NNRTIs and 42% to PIs), with 10% samples resistant to drugs on all three classes. Two-class resistance was observed in 23% (NRTIs and PIs), 13% (NRTIs and NNRTIs) and 5% (NNRTIs and PIs). Finally single class resistance was in 25% to (NRTIs), 7% to (NNRTIs) and 5% to (PIs). NRTI-resistant isolates were essentially resistant to 3TC (83%) but totally susceptible to ABC and TDF. All NNRTIs-resistant variants had cross-resistance to NVP. PIs-resistant isolates showed resistance to IND (100%), RTV (100%), NFV (50%) and SQV/RTV (25%) and susceptibility to APV, LPV, ATV and APV/RTV.

Discussion: Although the majority populations of viruses in Tunisian patients failing therapy are resistant to several antiretroviral administered drugs, they still susceptible to other non-available NRTI and PI molecules. Than eventual salvage therapeutic options exists but they are not accessible.

The study proved that for an optimal drug resistance monitoring of the emergence of, we do to use of more sensitive resistance test, to expand utilisation of resistance testing and increase treatment options.

PP 4.56.

Relative Quantification of Human Immunodeficiency Virus type 1 proviral DNA in Patients undergoing Structured Treatment Interruption

Kabamba-Mukadi B, Henrivaux P, Ruelle J, Bodeus M and Goubau P.

Université Catholique de Louvain, Bruxelles, Service de Médecine interne, Clinique Saint Joseph, Liège, Belgium.

Background: HIV-1 DNA proviral load pattern may be useful to monitor disease progression, long-term therapy efficacy and to select the best time for the STI institution.

Methods: A relative quantification assay of HIV-1 proviral DNA by LightCycler® real-time PCR based on SYBR Green I detection was developed in comparison to the number of purified CD4+ cells as estimated by the quantification of b-globin gene. The 8E5 cell line containing a single defective copy of HIV-1 proviral DNA was used as a standard for both genes. The ability of the designed gag primers to quantify HIV-1 Group M reference isolate subtypes A, B, C and D was assessed and showed similar PCR efficiencies with respectively slope values of -3.50, -3.37, -3.43 and -3.54. No amplification was obtained with HIV-2 ROD and EHO reference strains. The lower limit of quantification was 50 HIV-1 DNA copies per CD4+ cell sample. The dynamic range was within 50 and 106 HIV-1 DNA copies per CD4+ cell sample with intra- and inter-assay coefficients of variability ranging from 11,6% to 37,7%. We observed an inhibition phenomenon of the human b-globin reference gene amplification solved by diluting (10-fold) DNA from patient samples. The assay was applied on samples from fifteen patients undergoing 2 years of structured treatment interruption (STI). At the initiation of STI, out of the 15 STI patients, 11 patients had HIV-1 RNA viral load <50 copies/ml, 4 had a baseline HIV-1 RNA viral load <572 copies/ml (median of 2 log copies/ml) and the mean CD4+ cell count was 748 X 106 cells/L. The mean steady state plasma viral load after STI was about 3,2 log copies/ml and a mean CD4+ cell count of 717 X 106 cells/l. All STI patients had received previous monotherapy or dual therapy before highly active antiretroviral therapy (HAART) for a mean treatment total time of five years. Out of the 15 STI patients, all 7 patients with low plasma steady state viral load showed a DNA proviral load under 2,5 log copies/106 CD4+ cells, including 4 patients with a proviral load under the limit of quantification (<5 DNA copies/PCR). Out of the remaining 8 patients presenting a high plasma steady state viral load (>3,9 log copies/ml) 3 showed a DNA proviral load under 2,5 log copies/106 CD4+ cells while 5 had DNA proviral load above 2,5 log copies/106 CD4+ cells. A correlative tendency was observed between DNA proviral load and RNA steady state viral load in 85% of STI patients. We observed that to achieve undetectable plasma viral load at therapy initiation, patients for whom it was necessary to change antiretroviral treatment or in whom the time was longer, the proviral load was >2,5 log copies/PCR and the plasma viral load rebound was high. But a large and prospective study is needed to confirm this observation.

Conclusion: in patients undergoing STI, the HIV-1 DNA proviral load pattern may help to select the best time for the STI institution and predict the long-term viral replication control.

PP 4.57.
Safety Assessment of Patients Receiving Atazanavir (ATV) With Ritonavir (RTV), ATV With Saquinavir (SQV), or Lopinavir (LPV)/RTV: 48-Week Results From BMS AI424-045

Clotet B, Lazzarin A, Grinsztejn B, Lichtenstein K, Sankoh S and Wilber R. IrsiCaixa Foundation, Barcelona, Spain; S. Raffaele Hospital, Milan, Italy; Instituto de Pesquisa Clínica Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil; University of Colorado Health Sciences, Denver, CO; Bristol-Myers Squibb, Wallingford, CT, USA
Authors: B Clotet¹, A Lazzarin², B Grinsztejn³, K Lichtenstein⁴, S Sankoh⁵ and R Wilber⁵

Affiliations: 1IrsiCaixa Foundation, Barcelona, Spain; 2S. Raffaele Hospital, Milan, Italy; 3Instituto de Pesquisa Clínica Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil; 4University of Colorado Health Sciences, Denver, CO; 5Bristol-Myers Squibb, Wallingford, CT

Background: ATV is a potent once-daily PI that has durable efficacy with a favorable metabolic and tolerability profile compared to other protease inhibitors.

Methods: This study was a prospective, multinational, open-label study in treatment experienced patients randomized (1:1:1) to ATV/RTV 300/100 mg qd, ATV/SQV 400/1200 mg qd, or LPV/RTV 400/100 mg bid, each combined with tenofovir 300 mg qd and 1 NRTI. AEs and other safety parameters were evaluated.

Results: 358 patients randomized; 347 treated.

*Patients on lipid-lowering therapy excluded; no effect of on-study NRTI (eg, didanosine, stavudine) observed in multiple regression analyses.
†P<0.005 ATV regimens vs LPV/RTV, ‡P=0.04 vs ATV/SQV, §P=0.001 vs ATV/RTV, ¶P<0.05 vs ATV/RTV, and P=0.01 vs ATV/RTV.

	ATV/RTV N=119	LPV/RTV N=118	ATV/SQV N=110
Grade 2-4 related AEs (in □5% of patients)	% of Patients		
Total	29	25	26
Diarrhea	3	11¶	6
Jaundice	6	0	2
Nausea	3	2	8
Vomiting	0	<1	4
Scleral icterus	3	0	0
Grade 3-4 laboratory abnormalities	% of Patients		
Total bilirubin	49	<1	20
ALT/SGPT	4	3	4
AST/SGOT	3	3	2
Lipids	Mean % change, baseline to Week 48*		
Total cholesterol	-8	+6†	-4
HDL cholesterol	-7	+2	+4
Fasting LDL cholesterol	-10	+1	-3
Fasting triglycerides	-4	+30†	-14
Concomitant medications	% of Patients		
Antidiarrheal	6	24‡§	13
Lipid lowering	8	19¶	12

Discontinuations due to AEs were infrequent and comparable across cohorts. No patient discontinued because of elevated bilirubin levels or associated clinical symptoms.

Conclusions: All regimens were safe and well tolerated. ATV, when boosted with RTV or combined with SQV, demonstrated a significantly improved lipid profile over LPV/RTV with respect to total cholesterol and fasting triglycerides. Consistent with the observed AE profiles, patients receiving ATV-containing regimens were less likely to be administered concomitant antidiarrheal or lipid-lowering agents.

PP 5.1. CRF01_AE (subtype E) Gag Specific T-lymphocyte Responses In HIV-Infected Individuals Differ From That In Highly Exposed But HIV-Seronegative Individuals In Thailand

Sriwanthana B, Jitjuk B, Wichukchinda N, Rojanawiwat A, Tanaka M, Pathipvanich P, Ariyoshi K, Sawanpanyalert P. National Institute of Health, Nonthaburi, Lampang Hospital, Lampang, Thailand
Background: Identification of HIV-1 Cytotoxic T lymphocyte (CTL) epitopes is essential for the design and evaluation of candidate HIV preventive/therapeutic vaccines in Thailand, where host genetic backgrounds and strains of circulating HIV-1 are different from those in other parts of the world.

Methods: Fifty untreated HIV-infected individuals with a high CD4 count of over 200/ul and a plasma viral load ranging from <1,000 to 600,000 RNA copies /ml, and 19 highly exposed but HIV-seronegative (ESN) spouses of HIV-infected individuals were recruited from a HIV Cohort in northern Thailand from August to December 2003. Fresh PBMCs were examined for HIV-1 Gag specific T-lymphocyte interferon gamma production in an enzyme-linked immunospot assay (ELISpot) using 10 amino-acid overlapping 15-mer peptides, designed based on the most common CRF01_AE Gag sequences among 99 gag clones isolated from 45 cohort patients. Ten peptides were pooled in a Matrix way. Responses with 4 times over the background in triplicate experiments were considered positive.

Results: Cellular responses to one or more Gag peptides were detected in 33 of 50 (66%) infected persons and 5 of 19 (26%) ESN. Twenty-four (72.7%) of 33 infected persons with a significant response, recognized multiple peptides whereas 3 of 5 ESN with a significant response, recognized a single peptide. There was no significant association between the pattern of cellular responses and viral load. Using the Matrix approach, we identified 6 different peptides (3 among infected and 3 among ESN persons), of which 5 peptides potentially convey a new CRF01_AE Gag E CTL epitope. Intriguingly, ESN recognized peptides that were rarely recognized by infected persons; two peptides recognized by our ESN persons coincidentally convey CTL epitopes (KRWILGLLNK, IILGLNKIVR) that were recognized by ESN persons in Africa (Rowland-Jones 1998 and Kaul 2001).

Discussion: Our results indicate that cellular responses specific to CRF01_AE Gag exist in both HIV-infected and ESN Thais. The pattern of CTL recognition among ESN does differ from that in infected persons.

Our data may be relevant to understanding immune correlation to protection and development of effective vaccines.

PP 5.2.

Effects of Exogenous Nef Protein on Immune System

Pugliese A, Petrini S, Beltramo T, De Checchi S, Gallo G & Vidotto V. Department of Medical and Surgical Sciences, Section of Clinical Microbiology of Turin University, "Amedeo di Savoia" Hospital, Turin, Italy

We have studied the effect of recombinant Nef protein (American Biotechnologies, Inc. - ABT - Cambridge, Ma, USA) on in vitro some biological phenomena, directly or indirectly implicated in the immune response, i.e. different cellular receptors expression, apoptosis, macrophage phagocytosis, Interleukin (IL) 18 production. In particular dose dependent reduction of CD4 receptor surface expression paralleled with that of CXCR-4 in MT-4 T lymphocytic cells. Moreover this phenomenon was accompanied by the reduction of cell rate replication and by the increase of apoptotic levels of T lymphocytes. Recombinant Nef protein can also decrease Transferrin receptor (CD71) expression, especially in H9-V T cell line, a chronically HIV-1 - infected T lymphocytes (about of 36% with the dose of 1 µg/ml of Nef - $p < 0.01$ and of over 50% with 2.5 µg/ml). Besides recombinant Nef protein reduces the monocytic macrophage cells phagocytosing activity against *Candida albicans*, an opportunistic yeast that often seriously complicates HIV-infection, and also the phagocytosis of immune cells apoptotic bodies (ab). In particular, in the last case 3.8 ± 2.7 ab were phagocytosed per cell in absence of Nef and 0.4 ± 0.6 in presence of 1 µg/ml of protein ($p < 0.001$). In fact, immunocompetent cells more easily go in apoptosis, and so its ab can increase inflammatory phenomena. Finally recombinant Nef protein in an in vitro model consisted of THP-1 monocytoïd cells (spontaneously producing detectable levels of IL-18), may reduce the secretion of this cytokine ranging from the dose of 0.31 µg/ml (9% of reduction) and particularly with the dose of 1.25 µg/ml (69% of reduction, $p = 0.01$). This is of relevant interest because IL-18 is a proinflammatory cytokine, but have too an important function on the restoration attempt of Th1?Th2 T lymphocytes equilibrium.

PP 5.3.

Construction of Candidate DNA-Vaccines against HIV

Babkina IN, Pozdnyakov SG, Ryazankin IA, Babkin IV, Shchelkunov S.. State Research Center of Virology and Biotechnology "Vector", Koltsovo, Novosibirsk region, Russia

The goal of this project is to design anti-HIV DNA vaccines and vaccines involving recombinant vaccinia viruses. To reach this goal, genetic engineering techniques were used to construct several variants of expression plasmids with artificial gene TBI or gene gp120. We plan to design recombinant live polyvalent vaccines using vaccinia virus vector. Variants of recombinant virus with the following genes ENV2 (gp120dV3 with deleted V3 loop), STB-I, STBI?anchor, IL-2, TBI?HBsAg, TCI, and TCI?HBsAg will be obtained. The variants of TBI gene, encoding four T cell epitopes and five B cell epitopes, were inserted into the plasmid pBKRSV, pcDNA3.1-mycchislacZ(-). The plasmid pDOLHIVenv was used to obtain several plasmid constructs, expressing various variants of HIV-1 env gene. Recently, a new artificial T cell immunogen, TCI, was constructed. It contains about 80 CTL epitopes, selected from the HIV Molecular Immunology Database. We plan to design recombinant live polyvalent vaccines using vaccinia virus vector, containing the different genes. All the genetic constructs obtained will be studied in animal models.

PP 5.4.

Poly-CTL Epitope Immunogen, Candidate for DNA-vaccine against HIV-1

Bazhan SI, Belavin PA, Seregin SV, Danilyuk NK, Babkina IK, Karpenko LI, Nekrasova NA, Lebedev LR, Ignatyev GM, Agafonov AP, Ilyichev AA. SRC VB Vector; Koltsovo, Novosibirsk Region, Russia

An artificial T cell immunogen (TCI) has been designed as a candidate DNA-based HIV-1 vaccine using CD8⁺ CTL and CD4⁺ Th epitopes from main HIV-1 proteins Env, Gag, Pol and Nef. The protein 392 amino acids in length contains about eighty CTL-epitopes, which are totally restricted by ten different HLA class I molecules. To be able to detect CTL responses induced by a DNA vaccine in experimental animals, additional epitopes, restricted by mouse and Macaque rhesus IĪĪ class I molecules, were included in the target immunogen. The gene encoding the TCI protein was expressed in prokaryotic and eukaryotic systems. The presence of HIV-1 protein fragments in the immunogen structure was confirmed by ELISA and immunoblotting using panels of HIV-1-positive sera and monoclonal antibodies to p24. It has been demonstrated that eukaryotic recombinant plasmid pcDNA-TCI can induce both specific CTL responses and specific antibodies in immunized mice. It means that DNA-immunization incorporates all stages required for delivery of the target immunogen to the immune system: expression of TCI gene, processing of the target protein, and presentation of the resulting peptides in complex with MHC class I molecules to CD8⁺ CTL. Two systems have been examined for delivery of DNA vaccine encoding TCI immunogen. One is intended for i.m. injection and is in the form of an artificial virus like particle (VLP) containing plasmid pcDNA-TCI encapsulated within a spermidine-polyglucin conjugate. The other is intended for mucosal immunization and is based on attenuated *Salmonella typhimurium* strain 7207, which can deliver pcDNA-TCI directly into professional antigen-presenting cells. After immunization, the VLP and recombinant *Salmonella* induced an enhanced HIV specific serum antibody, proliferative and CTL responses in comparison with those induced by naked pcDNA-TCI. The most significant responses were produced when pcDNA-TCI was delivered by *Salmonella*.

PP 5.5. Mimotopes of Human Immunodeficiency Virus Type 1 Diagnostic and Neutralizing Envelope Epitopes

Gazarian K, Palacios Y, Gazarian T, Mailuf A. Mexican Nacional Autonomous University, Mexico City, Mexico; Regional Hospital Gabriel Mancera, Mexico City, Mexico

Introduction

The HIV-1 env subunits or their synthetic peptide versions are used for diagnosis and vaccination purposes. Epitope mimics selected in combinatorial phage-peptide libraries by infected host antibodies may better reflect properties of native viral epitopes

Material and Methods. Using sera of patients with disease progression prior to and after HAART, we select collections of mimotopes of the major HIV-1 epitopes, the gp41 CSGKLIC loop epitope ("CKC") of diagnostic value and broadly neutralizing epitopes of V3 loop and ELDKWA.

Results.

CKC mimotopes. Sera of 2 out of 5 patients before HAART, and after 4-week HAART retrieved in a 12mer library a collection of 21 peptides, all with CxxKxxC motif, perfectly mimicking the structure and binding specificity of the natural epitope. The best mimic

LPQQACLGKLLC derived by both patients mimics the epitope core **CSGKLIC** and by its LPQQA mimics the epitope C-terminal site **DQQL**. Mice immunized with this mimic generated the same specificity antibody as possessed the patients. The collection of phage-displayed CKC peptides present the whole range of the potential antigenic variations of this actually 100% conserved immunodominant HIV-1 epitope, and are better reagents for diagnosis of HIV-1 infection than are used now synthetic peptides.

Mimotopes of V3 crown GPGR epitope have not been isolated from peptide libraries screened with patient serum. We succeeded in isolation of several mimics of the GPGR. The most remarkable in these mimotopes is that anti-sera raised by them in mice show a wider cross-reactivity with different origin V3 loop sequences than does the patient anti-V3 antibody. Isolation of more such peptides is in progress to look for their potential in eliciting broad anti-V3 effects.

Attempts to isolate by means of patient serum mimotopes of the broadly neutralizing ELDKWA epitope as well as of an unknown epitope of the Tat are in progress.

Conclusion. Mimotope collections selected by antibodies of patients infected with HIV-1 are sources of information on functional viral epitopes and promise to become new generation antigens for designing protective vaccines with broad neutralizing potential.

PP 5.6.

Different Delivery Systems for Artificial Polyepitope HIV-1 Antigen

Nekrasova N A, Ignatyev G M., Agafonov AP, Lebedev LR, Ilyichev A A, Karpenko LI.

The State Research Center of Virology and Biotechnology "VECTOR" Koltsovo, Novosibirsk Region, Russia

nadinnekrasova@ngs.ru

One of the perspective approaches to the development of effective and safe vaccines is based on designing of synthetic polyepitope antigens. These vaccines consist of high immunogenic viral epitopes and will have none of the many drawbacks that are inherent to those based on native viral. In this work we investigated the immunogenicity of artificial polyepitope protein named TBI (T and B cell epitopes containing immunogen). The amino acids sequence of the TBI protein includes five B-cell neutralizing and four T-cell epitopes (all length 145 a.a.). It has been demonstrated earlier that TBI protein induces both HIV-specific cellular and humoral viral neutralizing response. However TBI has a low molecular weight and consequently is weak immunogene when injection alone. For increasing of TBI immunogenicity it is necessary to use Freund's adjuvant or alternative delivery system.

In this work for delivery of TBI protein we used artificial virus like particles and attenuated Salmonella strain. Comparative analysis of immunogenicity of vaccines constructions was carrying out. It has been shown, that all constructions are capable to induce both T cell and virus-specific antibodies responses in immunized animals. Serum of immunized mice displayed HIV-1 neutralizing activity. It is noted when we used recombinant Salmonella strain specific anti-TBI antibodies were determined not only in the serum of animals, but also in the intestine tissue. The use of virus like particle and attenuated Salmonella strain for delivery artificial protein TBI allows to enhance immunogenicity of vaccine construction.

PP 5.7.

Effects of Poly-glycine Linker on the Presentation of the Foreign Epitopes

Shahrokhi N, Bouzari S, Jafari A.

Pasteur Institute of Iran, Tehran, Iran

The aim of the construction of fusion proteins is the presentation of small epitopes on the surface of the carrier proteins to make a multivalent immunogen or enhance the immunogenicity of the foreign epitopes. An important consideration in the construction of active and stable fusion proteins is the correct folding and minimal effects of carrier and foreign epitopes on each other.

Core particle of the hepatitis B virus (HBV) potentiate the immune response against foreign epitopes presented on their surface. However, in most cases insertion of a heterologous epitope in the permissible sites within the core antigen results in reduction in immunogenicity of the carrier which is undesirable when immunogenicity of the both components of the chimeric protein is required. Therefore, gene coding for 'a' determinant of HBsAg were inserted in c/e2 epitope of core gene with and without poly-glycine linkers and expressed in human embryonic kidney cells (HEK cells). Hybrid HBc core protein harboring 'a' determinant flanked with poly-glycine retained HBcAg and HBsAg antigenicity. In contrast, insertion without poly-glycine abrogated recognition of hybrid HBcAg/s with anti-HBc and anti-HBs antibodies. Expression of both glycosylated and nonglycosylated form of the chimeric protein was observed in the cell lysate and the difference between the apparent molecular weight of the HBcAg and the chimeric protein was in good agreement with the amino acid sequence encoded by the insert. Intramuscular injections of 100 µg of the plasmid DNA expressing hybrid HBcAg/s induced humoral immune responses against native HBcAg and HBsAg in mice and cellular response against native HBcAg. These results indicate that the use of poly-glycine linker could help the correct formation of hybrid proteins and surface accessibility of the foreign epitopes.

PP 5.8. Chimeric Core Particles HBcAg Carrying Epitopes from Pres Region of HBV Surface Protein

Veremeiko TA, Lebedev LR, Zaitsev BN, Nekrasova NA, Ilyichev AA, Karpenko LI
The State Research Center of Virology and Biotechnology "VECTOR" Koltsovo, Novosibirsk Region,
Russia
veremeiko@mail.ru

Many studies have provided evidence that core antigen of hepatitis B virus (HBcAg) is extremely immunogenic and thus may be a promising candidate for hepatitis B virus (HBV) vaccine, but antibodies induced by HBcAg immunization is not protective. It is known that HBcAg is also an effective carrier for heterologous epitopes. Because it is able to self assemble into virus like particles, which expose heterologous epitopes on its surface as numerous copies. Here we constructed chimeric HBcAg carrying HBV surface protein epitopes. We introduce amino acid sequence 27-37 of preS1 and 131-145 of preS2 region HBV surface protein into immunodominant HBcAg epitope. The chimeric proteins assemble to particles. We showed reduced HBcAg antigenic properties of chimeric HBcAg. Balb/c mice were immunized intramuscularly by HBcAg carrying preS region epitopes with Freund's adjuvants or without. Chimeric core particles induced immune respond in Balb/c mice.

PP 6.1. Helinx® Technology Inactivates High Titers of SARS-CoV, WNV and Vaccinia in Platelet Concentrates

Dupuis K, Sampson-Johannes A, Bernard K, Sawyer L.

Cerus Corporation, Concord, CA; New York State Dept. of Health, Slingerland, NY, USA

Background: Helinx® technology, as used in the INTERCEPT Blood System, was developed to address the problem of pathogen contamination, especially bacterial contamination, of platelet concentrates (PC). The technology utilizes amotosalen HCl and UVA illumination, and has been demonstrated to inactivate a wide variety of blood-borne pathogens in platelets, including enveloped and non-enveloped viruses, gram negative and gram positive bacteria, and parasites. Presented here are the results of recent investigations of the efficacy of this treatment against viruses of emerging concern in the blood supply; the agent of severe acute respiratory syndrome (SARS-CoV), West Nile virus (WNV) and vaccinia virus (VV). A summary of previous inactivation data for a number of bacterial, viral and parasitic pathogens will be provided in the poster.

Methods: For SARS-CoV and VV studies 30 mL platelet aliquots were prepared from single donor apheresis platelets. The WNV studies utilized full-size (~300 mL) PC units. PC collected in 37% plasma/63% platelet additive solution (PAS III) were inoculated with virus to a final concentration of ~106 pfu/mL, then treated with 150 µM amotosalen HCl and 3.0 J/cm² UVA. SARS-CoV and WNV were treated with a single 3.0 J/cm² UVA treatment, VV was treated with a single 1.0 J/cm² and cumulative 2.0 J/cm² and 3.0 J/cm² UVA treatments. Samples were taken prior to illumination to determine input titer and immediately after illumination to detect any residual viable virus. Titers were determined by plaque assay on Vero (WNV and VV) or Vero E6 cells (SARS-CoV). **Results:** See table below. A standard deviation was not calculated for the log reduction of SARS-CoV because only two replicate experiments were performed.

Conclusions: SARS-CoV, WNV, and vaccinia in platelet concentrates were all inactivated to below the limit of detection by treatment with 150 µM amotosalen HCl and 3.0 J/cm² UVA.

Inactivation of Viruses of Emerging Concern in Platelet Concentrates Using 150 µM Amotosalen HCl and 3.0 J/cm² UVA Treatment

Virus	Strain	Number of Replicates	Log Reduction (Mean ±SD)
SARS-CoV	Urbani	2	>6.3
WNV	Lineage 1 (pFLWNV)	4	>6.0 ±0.4
Vaccinia	IHD-W	3	>5.2 ±0.2

PP 6.2.

Chinese Herbal Medicine for Severe Acute Respiratory Syndrome (SARS): a systematic review and meta-analysis

Liu JP, Manheimer E, Shi Y, Gluud C.

Liverpool School of Tropical Medicine

Liverpool, UK ; University of Maryland School of Medicine, Baltimore, USA; Shanghai University of Traditional Chinese Medicine, Shanghai, China; Copenhagen University, Copenhagen, Denmark

Background Severe acute respiratory syndrome (SARS) poses a great challenge to international healthcare. Chinese medicine combined with conventional medicine has been used to treat more than half of the SARS patients in China. To ensure appropriate practice and policy, we reviewed the beneficial and harmful effects of the combined therapy in randomised clinical trials systematically.

Methods We searched The Cochrane Library, PubMed, Chinese Biomedical Database, trials database of the Cochrane Collaboration Complementary Medicine Field, Chinese Journals Full-text Database, Chinese Scientific Journal Database, and the Allied and Complementary Medicine Database (AMED) from November 2002 through February 2004. We identified randomised clinical trials comparing herbal medicines with conventional medicine against conventional medicine alone for treating SARS. Methodological quality of trials was assessed according to the Cochrane Collaboration guideline. Non-randomised controlled studies were included in exploratory analysis.

Results Eight randomised trials (n=488 patients) were identified. The methodological quality was generally low. The pooled results showed that herbal medicines combined with conventional medicine had significant beneficial effect on mortality (relative risk 0.32, 95% confidence interval (CI) 0.12 to 0.91). Pooling data from six non-randomised controlled studies showed a similar beneficial effect of combined therapy (0.27, 0.12 to 0.61; n=486). The combined therapy resulted in shorter duration (days) of fever clearance (weighted mean difference -0.83, 95% CI -1.30 to -0.35), symptom relief (-1.23, 95% CI -2.09 to -0.37), and resolution of chest radiograph abnormalities (-2.61, 95% CI -3.74 to -1.49), as well as a reduction of secondary fungal infections in patients receiving glucocorticoids (relative risk 0.35, 95% CI 0.14 to 0.90). Adverse events from the herbal medicines were not reported.

Conclusions Chinese herbal medicine combined with conventional medicine may have beneficial effects in SARS patients. The evidence is not compelling because of small sample size, low methodological quality, and varying use of different herbs. Further well-conducted randomised clinical trials are needed.

PP 6.3.**Mucosal Immunogenicity of Surface-displayed SARS Viral Antigens on Lactic Acid Bacteria**

Kim CJ, Lee JS, Poo H, Sung MH. College of Veterinary Medicine, Chungnam National University, Bioleaders Corp., Korea Research Institute of Bioscience and Biotechnology, Daejeon, Korea, South

Introduction: Severe acute respiratory syndrome (SARS) is a newly emerging infectious disease caused by a novel coronavirus with high case-fatality proportion of 9.6%. Most coronaviruses first replicate in epithelial cells of the respiratory or enteric tracts and cause the mucosal diseases. It is necessary to induce the mucosal immunity to prevent the coronavirus infection. However, parenteral immunization could not provide proper protective immune responses at mucosal areas. We have developed a new surface-display motif from poly-gamma glutamic acid synthetase in *Bacillus subtilis* chunggukjang and applied to express the antigens of SARS-CoV on the surface of lactic acid bacteria as a GRAS (generally accepted as safe) organism. Aside from the ease of their use and low cost of manufacturing and distribution, an important advantage of mucosal bacterial vaccines is the possibility of inducing both mucosal and systemic immune response.

Methods: The cDNAs (nucleocapsid and spike protein genes of SARS-CoV) were prepared by PCR and cloned into the pHCE-pgsA expression plasmid containing the surface-display motif. The surface expression of nucleoprotein and spike proteins on Lactic acid bacteria was detected and verified by Western immunoblotting of fractionated cells and FACS analysis. After intranasal and per oral administration of mice with recombinant *L. casei*, serum IgG and mucosal IgA against specific N and S antigens were detected by ELISA.

Results: The surface expressions of N and S proteins as the fusion protein with pgs A motif were confirmed. The mucosal administrations of recombinant *L. casei* containing each proteins of SARS-CoV elicited high levels of systemic antibody (serum IgG) and mucosal antibodies (mucosal IgA antibody in intestinal fluid and lung lavages) against each antigen.

Discussion: The strategy developed in this study may make it possible to generate live oral vaccines to induce protective mucosal and systemic immune responses against emergent virus infection.

PP 6.4.

The Role of TT Virus (TTV) Infection in Human Pathology - the analysis of observed cases

Tomasiewicz K, Modrzewska R, Krawczuk G, Łyczak A. Department of Infectious Diseases Medical University of Lublin, Poland

The role of TT virus (TTV) in human pathology remains unclear. The virus was isolated for the first time in 1997 from blood of the patient with posttransfusion hepatitis. It has led to conclusion the virus is primarily associated with liver pathology.

The virus was isolated from different types of tissue, such as liver, bone marrow, lymph nodes, lung tissue, spleen, kidney, muscles and pancreas. These facts indicate the difficulties in exact assessment of the virus tropism.

At the Department of Infectious Diseases medical University of Lublin the test for TTV is done in patients with clinical and biochemical evidences of acute viral hepatitis, in whom serological and virological markers of common primary and secondary hepatotropic viruses are negative.

In the year 2003 blood specimens of 18 patients with acute hepatitis of unknown etiology were examine for TTV infection, using PCR method. The positive result was found in 9 patients.

In the day of hospital admission in all cases the levels of liver aminotransferase were markedly elevated. ALT levels ranged from 630 UL to 2945 UL (the normal level is up to 31 UL), mean 1376 UL $\pm$ 585 UL. AST levels were also highly elevated and ranged from 464 UL to 2275 UL, mean 1115 UL $\pm$ 492 UL. Despite of symptomatic and hepatoprotective treatment aminotransferase levels were elevated for more than 6 weeks after admission day. In 6 cases after 2 month these levels were more than 400 UL. In 5 cases normal values were observed after 5 month of treatment. In 1 case there were 2 episodes of exacerbation with aminotransferase levels more than 1000 UL and bilirubin level more than 10 mg/dl, and complete biochemical normalization was observed 9 month after the day of hospital admission.

Unfortunately, in 3 other cases, we had diagnosed 6 weeks later pancreas cancer. It should be stressed that at the time of hospital admission there were no symptoms and biochemical markers of cholestasis, and routine ultrasonography examinations, which were repeated at least twice did not show any pancreas pathology. In 1 patient with pancreas cancer we additionally discovered hepatitis G virus (HGV) infection.

The cases of acute hepatitis we present here should be treated as a preliminary report and the comment in the discussion about the real role of TTV in human pathology. In these cases, due to exclusion of any other known infection and of non-infectious pathology of the liver, TTV should be consider as an etiologic agent of acute hepatitis. The attention should be paid to long lasting elevation of aminotransferase level, but no signs of chronicity.

A special interest awakes 3 cases of pancreas cancer. Is that any relationship between TTV infection and oncogenesis in pancreas? This answer has no answer yet. We have not found any report concerning that problem. We think there is a need for further research under possible link between pancreas cancer and TTV infection. The theory that TTV has no medical significance because it is widespread in our opinion can not be the answer for controversial questions.

PP 6.5. Out of Africa: A Sorry Safari

Uslan DZ, MD and Sia IG. Mayo Clinic, Rochester MN, USA

A 62-year-old man presented to our institution with a one-week history of a non-pruritic left leg rash, low-grade fever, and tender inguinal adenopathy. He had traveled to the African countries of Malawi and Zambia for sightseeing and safari for the month prior to onset. He denied any insect exposure but did not use any specific topical prophylaxis. He took mefloquine for malaria prophylaxis. He was seen in the ER and prescribed cephalexin but the rash continued to worsen. Past history was unremarkable. He had received influenza, meningococcal, polio and yellow fever vaccines one month prior to travel. His other immunizations were up to date. On exam, the patient appeared well, with a temperature of 36.8 C. He had tender left inguinal lymphadenopathy. Just below his left knee was an approximately 1 cm black eschar. (Multiple pictures to be presented) Below this was a large area of erythematous skin with a petechial non-blanching rash. There was associated lymphangitic streaking extending up towards the inguinal area as well as significant unilateral pitting edema. The remainder of his exam was normal. Laboratory studies were unremarkable. Duplex ultrasound of the leg was negative for deep venous thrombosis. The patient's cephalexin was discontinued, and doxycycline was started empirically. His adenopathy resolved within 2 days. After approximately one week the rash began to fade and his lymphedema resolved. Rocky-Mountain Spotted Fever serology was positive at 1:512. As RMSF is not endemic to Africa, other specific rickettsial serologies were requested from a research laboratory. These revealed initial *R. africae* IgG of 1:32 with IgM of 1:8. This was rechecked one month later and revealed IgG of 1:256. Other rickettsial serologies were negative.

African Tick-bite fever (*Rickettsia africae*) is an increasingly common and appreciated cause of illness in returning travelers from Africa. In a recent study, 27% of patients returning from sub-Saharan Africa with fever were found to have *R. africae* infection. The infection is spread through the *Amblyomma* tick, a notoriously aggressive tick that is associated with wild game but may be found on vegetation. Common clinical characteristics are fever, headache, myalgias, lymphadenitis, and an inoculation eschar with cutaneous rash-the classic "tache noir." There is no readily available serologic diagnosis except in research laboratories, although patients will occasionally have positive serology for RMSF. The infection is usually self-limited but can be treated with oral doxycycline. Travelers to sub-Saharan Africa should be made aware of risks and educated about primary insect prophylaxis. This patient likely contracted *R. africae* while on safari in Zambia.

PP 6.6.

Association of a Novel Perforin Gene Polymorphism with HTLV-I Infection in Mashhad, North East of Iran

Farid R, Kharazmi A, Nobahar V.

Mashhad University of Medical Sciences, Mashhad, Iran

Background:

Human T Lymphotropic Virus I (HTLV-I)-specific cytotoxic T lymphocytes (CTL) recognizes the products of the HTLV-I Tax, in the context of HLA-A2 and kills their target through a perforin dependent mechanism. The efficiency of the CTL response may lead the HTLV-I infested individuals.

Materials and Method:

In this study we performed single stranded conformational polymorphism (SSCP) and DNA sequencing to analyse the promoter, 5' UTR and first intron of the perforin gene to identify novel polymorphism. Genotyping of patients with Human T-cell Lymphotropic Virus Type I-associated myelopathy or/ tropical spastic paraparesis (HAM/TSP), HTLV-I carriers and healthy controls was carried out to identify difference between these groups.

Results:

We detected a novel polymorphism in the first intron of the perforin gene at position +418°C/T, relative to the transcription start site. The frequency of the C allele was statistically significant increased in HAM/TSP patients compared with healthy control group ($P < 0.01$). Although the frequency of the C allele was higher in HAM/TSP rather than HTLV-I carriers that were no significant difference was observed between these two groups ($P = 0.09$). The allele frequency of +418°C/T polymorphism was the same in the HTLV-I carriers and healthy controls.

Conclusion:

We concluded that perforin +418°C/T polymorphism is associated with the outcome of HTLV-I infection.

PP 6.7. Clinical Profile of Dengue Outbreak in Delhi

Bhoi S, Kheira A, Wasir J.

All India Institute of Medical Sciences, New Delhi, India

Introduction: Recent years have seen dengue as an emerging infection with changing trends in its characteristics. This study highlights the clinical profile of Dengue outbreak in Delhi.

Material And Methods: All patients; who tested positive for either IgM or IgG and IgM anti-dengue antibodies were included in the study. Classical Dengue fever (DF), Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS) were defined as per WHO criteria. Statistical analysis was done by Epi Info 2002.

Results: 155 suspected cases of Dengue reported to the emergency department. 36 cases were excluded from the study, as they did not fulfill the inclusion criteria. Rest 119 cases were defined as DF in 58(48.7%), DHF in 53(44.5%) and DSS in 8(6.75%) cases. The mean age of patients with DF, DHF and DSS were 27 ± 8 , 26.7 ± 12 , 25 ± 12 yrs respectively. Males (78.9%) were affected more than females (21.1%). The predominant presentations were fever (100%), rash (24.3%), abdominal pain (16.8%), seizures (1.6%) and retroorbital pain (0.8%). Bleeding manifestations were observed in 56(47%) cases. Petichae (13%), hematemesis (10.9%), gum bleeding (10.08%), subconjunctival hemorrhage (9.24%) and multiple site bleeding (11.7%) were noted frequently. Other bleeding manifestations such as hematuria, bleeding per vagina, hemoptysis and intracranial hemorrhage were noticed in few cases. Hepatomegaly (15.9%), splenomegaly (2.5%), ascitis (7.6%), bradycardia (1.6%) and positive Hess test (0.84%) were the other clinical manifestations. The mean platelet count noticed in DF, DHF and DSS were 50 ± 27.4 , 46 ± 31.05 , 42 ± 26 $\times 10^3$ respectively. The major unusual feature observed was moderate (≤ 5 fold) elevation of transaminases, which started rising on the 3rd day, peaked on the 9th day and returned to baseline over a period of three to eight weeks. In DF, DHF and DSS; the mean serum bilirubin $[0.83 \pm 0.27, 0.89 \pm 0.3, 0.9 \pm 0.48]$ mg/dl ($p=0.9$), AST $[123 \pm 88.5, 120 \pm 93, 112 \pm 37]$ I.U., ALT $[108 \pm 48, 109 \pm 70, 107 \pm 36]$ I.U. ($p=0.01$) and serum alkaline phosphatase (SAP) $[138 \pm 53, 124 \pm 52, 153 \pm 26]$ I.U. ($p=1.7$) were noticed. USG revealed acalculous cholecystitis in 17% (DF), 2.8% (DHF) and 2.5% (DSS) cases. All patients recovered except one (0.84%); who succumbed due to intracranial hemorrhage.

Conclusion

Fever, rash, thrombocytopenia and anicteric hepatitis were the predominant manifestation. Statistically significant elevation of transaminases along with normal serum bilirubin and SAP was observed in all categories (DF, DHF, DSS); this is in contrast to previous reports where elevated transaminases were observed more frequently in DHF and DSS. These observations may be seen as a changing trend of Dengue virus infection, where impact on liver occurs irrespective of severity of the disease.

PP 6.8.

Comparison of HCV RNA and HCV Core Antigen Kinetics in the Follow-up of a Therapeutic Protocol in HCV-HIV Coinfected Patients (RIBAVIC)

Lunel F, Pivert A, Payan C, Morand P, and the members of the Ribavir Scientific Committee (ANRS HC02). Laboratoire de Bactériologie-Virologie, CHU Angers, France ; Laboratoire de Virologie, CHU Grenoble, France

Background: trak-C, developed by Ortho-Clinical Diagnostics, is an assay to quantitate total Hepatitis C Virus (HCV) core antigen in serum. The evaluation of trak-C assay was realised by comparison of the viral kinetics of both markers: total HCV core antigen (trak-C) and HCV viral load (Versant HCV RNA 3.0, Bayer Diagnostics). To evaluate this quantitative assay, we studied 206 patients from RIBAVIC protocol (1100 samples for each assay).

Methods: RIBAVIC is a therapeutic, multicenter, randomised trial comparing the efficacy of two treatments: Interferon alpha 2b (IFN) 3 MU x3/week and Ribavirin 800 mg/day versus Pegylated Interferon (PEG-IFN) 1.5 µg/kg/week and Ribavirin 800 mg/day during 48 weeks, in co-infected HIV-HCV patients naïve of HCV treatment. Patients were tested at week (W) 0, 2, 4, 12, 24, 48 and 72. Sustained virological responders have a negative PCR 6 months after the end of treatment (W72).

Results: Correlation of core antigen quantitation by trak-C and RNA quantitation by HCV RNA 3.0 was excellent ($r = 0.94$, $p < 0.01$). The study of viral kinetics show that both markers similarly move around during and after treatment of HCV, for Non Responders, Sustained Responders (SR) and Relapsers. We found a very good correlation between decrease of viral load and negativation of HCV core antigen under treatment: a 2 log IU/ml decline after W4 was significantly correlated with a negative HCV core antigen and sustained response ($r = 0.64$, $p < 0.01$). After W4, 69.5% of SR had an RNA decrease > 2 log IU/ml and 85.2% had a negative HCV core antigen (49.1% and 69% after W2). The positive and negative predictive values of response to the treatment at W4 were respectively 57.7% and 85.4% for viral load reduction > 2 log IU/ml, 56.5% and 91.1% for negative HCV core antigen, 88.9% and 79.1% for negative PCR ($p < 0.0001$).

Conclusions: Total HCV Core Antigen appears to be a new tool for monitoring patients with HCV-HIV co-infection and an early predictor of response to the treatment.

PP 6.9. Prophylactic and Therapeutic Effects of Small Interfering RNA Targeting SARS-Coronavirus

Zheng Bj, Guan Y, Tang Q, Cheng D, Xie FY, He ML, Chan KW, Wong KL, Lader E, Woodle MC, Lu PY, Li B, Zhong N.

Department of Microbiology, Institute of Molecular Biology, Department of Pathology, University of Hong Kong, Hong Kong, China

Objectives: To identify and characterize the siRNA duplexes that are effective for inhibition of SARS-CoV infection and replication in the non-human primate cells. This in vitro study will serve as the foundation for development of novel anti-SARS therapeutics.

Methods: 48 siRNA sequences were designed for targeting regions throughout entire SARS-CoV genome RNA including open reading frames for several key proteins. Chemically synthesized siRNA duplexes were transfected into fetal rhesus kidney (FRhK-4) cells prior to or after SARS-CoV infection. The inhibitory effects of the siRNAs were evaluated for reductions of intracellular viral genome copy number and viral titers in the cell culture medium measured by Q-RT-PCR and CPE-based titration respectively. Four siRNA duplexes were found to achieve potent inhibition of SARS-CoV infection and replication. A prolonged prophylactic effect of siRNA duplexes with up to 90% inhibition that lasted for up to 72 hours was observed. Combination of active siRNA duplexes targeting different regions of the viral genome resulted in therapeutic activity for up to 80% inhibition.

Conclusion: Chemically synthesized siRNA duplexes targeting SARS-CoV genomic RNA are potent agents for inhibition of the viral infection and replication. The location effects of siRNAs were revealed at both genome sequence and open reading frame levels. The rapid development of siRNA-based SARS-CoV inhibitors marked a novel approach for combating newly emergent infectious diseases.

PP 6.10.

An Exceptional Case Report of Very Early Tertiary Syphilis in a Young Adult

Manfredi S, Sabbatani S, Chiodo F. Infectious Diseases, University of Bologna, Bologna, Italy

An exceedingly rare episode of isolated lues encephalitis occurred in a 34-year-old otherwise healthy young woman, with a negligible medical history and negative syphilis serologic testing obtained a decade before (when our patient became pregnant), is described. On the ground of an isolated positive serological testing for *Borrelia burgdorferi* (later interpreted as a cross-reaction), and in consideration of a possible diagnosis of cerebral Lyme disease, early i.v. ceftriaxone treatment was initiated. Even after the diagnosis was corrected into that of a neurosyphilis, the initial antimicrobial therapy was continued, until it achieved complete clinical and microbiological success after 24 days of treatment in a Day-Hospital setting, and three subsequent weekly penicillin administrations. When considering the differential diagnosis, a luetic etiology should not be underestimated, when facing young patients with signs and symptoms of a meningoencephalitis. Our case report was characterized by an extremely low patient's age, compared with that typical of the occurrence of tertiary neurosyphilis. The diagnosis was finally confirmed by highly positive paired serum and cerebrospinal fluid serological examinations, including VDRL, FTA-ABS, and TPHA (this last test showing a titre of 1:2560 on serum, and 1:128 in the cerebrospinal fluid), together with some suggestive early clinical manifestations, like seizures, altered mentation, cognitive impairment, lip drop, and frank anisochoria. These concomitant clinical and laboratory findings, together with a neuroradiological (CT) report indicating a diffuse encephalitis, allowed us to confirm the diagnosis of neurosyphilis, despite a demonstrated, underlying cross-reaction with *B. burgdorferi* serology. Ceftriaxone treatment, although started under the suspicion of a borreliosis, acted favorably and allowed early discharge and an effective outpatient treatment. Although parenteral ceftriaxone benefits from its once-daily administration (and can be easily delivered on outpatient basis), it does not represent the first-choice treatment of neurosyphilis. However, our experience demonstrated a favorable and rapid response to ceftriaxone administration, in absence of adverse events and significant disease sequelae, after a 16-month follow-up.

PP 6.11. Favorable Long-term Management of a HIV-unrelated Brain Cryptococcoma with Voriconazole, after Fluconazole Failure

Manfredi R, Sabbatani S, Pavoni M, Consales A, Chiodo F.

Infectious Diseases, University of Bologna, and 1Department of Neurosurgery, Bellaria Hospital, Bologna, Italy

When considering cryptococcosis in a setting other than that of HIV disease, very few occurrences are documented, and central nervous system cryptococcoma represents an absolutely rare event. The authors refer on an exceptional case report of cerebral cryptococcoma occurred in a 46-year-old chronic nephropathic HIV-negative male subject suffering from homocystinuria, favorably cured with combined neurosurgery and voriconazole treatment, after a limited and not sustained response to high-dose fluconazole administration. When clinicians face an expansive cerebral mass, before starting any treatment it is necessary to establish an early presumptive and possibly ethiological diagnosis, in order to target antimicrobial treatment and to recommend eventual surgical drainage. Among a broad spectrum of infectious etiologies, it is suggested to take into careful consideration also of the hypothesis of a fungal abscess, whose evolution would certainly be disadvantaged by a symptomatic treatment with steroids (like happened in our patient before that a specific diagnosis was confirmed), and/or antibacterial agents. In our case, after surgical intervention giving a confirmed diagnosis of cryptococcoma, a first treatment line carried out with i.v. fluconazole did not lead to a sustained improvement, as the new antimycotic derivative voriconazole did at 400 mg/day, later in the disease course. In our case, both surgical and medical treatment of a brain cryptococcoma in a non-HIV-infected patient have been performed: the surgical management helped to remove the majority of the brain abscess and to formulate the diagnosis, as well as to release an initial hydrocephalus. After patient's death due to a underlying progressive renal-vascular disease, necropsy examination of the cerebral parenchyma did not shown any sign of infiltration due to *Cryptococcus neoformans*; voriconazole administration can be therefore considered eradicating in this clinical setting. Also in HIV-infected subjects, a cryptococcoma is a relatively rare feature, and it hardly appears isolated, and not associated with a meningeal cryptococcosis. As far as we know, there are no prior reports of primary cryptococcomas in chronic nephropathic, and HIV-negative subjects, as well as in patients with homocystinuria. The authors underline that, although being still a rare occurrence, cerebral cryptococcoma is expected to represent an emerging issue in the next future, because of its relationship with a broadening range of supportive risk factors, including malignancies, leukopenia-neutropenia, end-organ (i.e. kidney) failure, bone marrow and solid organ transplantation, and multiple underlying causes of primary or secondary immunodeficiency. With the mounting increase in the frequency of patients with end-organ kidney disease, it is possible that also cryptococcosis may emerge as a more frequent complication in the next future.

PP 6.12.

Clinical and Microbiological Features of *Capnocytophaga* spp. As an Emerging Pathogen in Brain Abscess

Manfredi R, Sabbatani S, Frank G, Chiodo F.

Infectious Diseases, University of Bologna, and Department of Neurosurgery, Bellaria Hospital, Bologna, Italy

The etiology of brain abscess includes a broad spectrum of potential pathogens: gram-positive, gram-negative, anaerobes, and fungi. The major predisposing conditions include otitis, mastoiditis, lung abscess or empyema, dental abscess or granuloma, trauma or neurosurgery, prior meningitis, endocarditis, and bacteremia from distant sources, so that a polymicrobial origin and a mixed flora cannot be excluded. *Capnocytophaga* is a genus in the family Cytophagaceae, including fastidious gram-negative microorganisms needing an increase of CO₂ concentration to enhance in vitro growth. Only anecdotal cases of central nervous system infection (meningitis and more infrequently abscess or subdural empyema), have been reported to date. *Capnocytophaga* spp. organisms are difficult to be isolated and identified (and are consequently underestimated in clinical practice), so that they are infrequently tested for antimicrobial susceptibility. As a consequence, extensive and updated in vitro sensitivity studies of these organisms are lacking. Penicillins and derivatives (or third-generation cephalosporins for endocarditis and meningitis), plus aminoglycosides, are considered the first-line choice, although results of aminoglycoside, cotrimoxazole, and metronidazole adjunct to beta-lactams are unpredictable, based on different in vitro assays and clinical reports. Surprisingly, also compounds usually active against gram-positive organisms (including erythromycin, clindamycin, rifampin, tetracyclines, cotrimoxazole, chloramphenicol, fluoroquinolones, and even glycopeptides), test effective against the majority of *Capnocytophaga* spp. organisms. The fourth case report of a brain abscess due to the fastidious gram-negative organism *Capnocytophaga* spp. is described and discussed on the ground of the available clinical, microbiological, and therapeutic literature evidences. A probable origin from a cat bite and/or an underlying severe mandibular granuloma is suspected. Due to lack of clinical and neuroradiological response to neurosurgery and a full-dosage imipenem-amikacin-clindamycin-fluconazole association, a second-line empiric linezolid treatment at 1200 mg/day proved rapidly successful, in absence of further microbial yield. Despite the isolated culture of an infrequent and fastidious gram-negative pathogen from purulent material of a brain abscess, patients with underlying risk factors and recent surgery may be exposed to a polymicrobial infection including also resistant gram-positive cocci. Due to its favorable brain penetration and its dual mode of administration, linezolid may be an alternative option for patients with multiple risk factors, brain abscess of suspected polymicrobial origin, and lack of response to empiric or culture-driven therapeutic attempts. In the management of a brain abscess where the role of gram-positive cocci or other pathogens with unpredictable antimicrobial sensitivity is highly suspected, a correct treatment has to be targeted on multiresistant organism, pending in vitro sensitivity assays. When considering the intrinsic limit represented by the blood-brain barrier, the therapeutic efficacy of glycopeptides in the cerebral district is limited by their 5-15% cerebrospinal fluid transfer. The recent availability of oxazolidinone and streptogramin derivatives broadens the spectrum of antimicrobial agents effective against the emerging strains of multiresistant and glycopeptide-resistant gram-positive cocci and other organisms, although in vitro data on the activity of these compounds on *Capnocytophaga* spp. organisms are still lacking. The indications of linezolid include severe bacterial central nervous system infection where a multiresistant gram-positive etiology is suspected.

PP 6.13. Emerging Severe Central Nervous System Infections, and Potential Role of Linezolid Administration in Three Different Clinical-microbiological Scenarios

Manfredi R, Sabbatani S, Frank G, Chiodo F.

Infectious Diseases, University of Bologna, and Department of Neurosurgery, Bellaria Hospital, Bologna, Italy

The emerging of antimicrobial-resistant gram-positive cocci in the setting of surgery and intensive care units, recommends particular attention in the selection of effective therapeutic choices, leading to overcome both microbial resistances, and hemato-encephalic barrier to an effective local drug penetration. In Italy the occurrence of methicillin-resistant *Staphylococcus aureus* proves particularly elevated, especially when high-risk patients and/or settings are of concern. Three representative case reports (two brain abscesses and one post-surgical meningitis), are presented and discussed: in all these cases a salvage linezolid treatment proved resolutive. The first reported case has its major interest in the isolation from purulent abscess material of a rare gram-negative oxidase-negative bacillus. A slowly progressive central nervous system (CNS) involvement was noticed, compared with the literature-quoted dramatic-fulminant course typical of immunocompromised patients. Probably the absence of an underlying immunosuppression, and combined surgical-antibiotic therapy, prompted clinical and microbiological success of this unusual localization of *Capnocytophaga* spp disease. Moreover, the complicated and relapsing course of our patient might suggest a polymicrobial infection. Should the first-line treatment allowed microbial eradication, linezolid achieved complete resolution of CNS abscess, which did not ameliorate after over 3 weeks of combined imipenem-amikacin-fluconazole administration, preceded by surgical drainage. In the second case report, we could not rely on a culture isolation of clinical specimens, probably due to the prolonged antimicrobial therapy preceding neurosurgery. Because of a need of an empirical combination, the post-operative therapy was conducted with linezolid and imipenem. The result proved strategically favorable, since after the improvement of neuro-radiological picture, medical treatment was continued with oral linezolid only, avoiding i.v. administration and accelerating patient discharge. With our third presented case, we underline the clinical-therapeutic evolution of a patient who developed a post-surgical nosocomial purulent meningitis, failed to respond to a 3-drug association of vancomycin, imipenem, and gentamicin, and had a very favorable and rapid (10-day) course only after linezolid administration, in absence of relapses or sequelae. A post-surgical infection caused by multiresistant gram-positive agents may be strongly hypothesized, on the ground of prior therapeutic failure, and immediate response to linezolid. Therapeutic options for CNS infection are still limited, and the prognosis remains severe, especially when gram-positive infection is of concern. Moreover, enterococcal disease usually complicates the course of chronic underlying illnesses, non-HIV-associated immunodeficiency, head trauma, and complicated neurosurgery. In the treatment of post-neurosurgical cerebral abscess and meningitis, a key issue is represented by the low cerebrospinal fluid concentration of the available glycopeptides, usually recommended as first-line therapy of resistant gram-positive cocci. Evidences from the literature recently focused on the possible role of linezolid as a favorable candidate for the treatment of severe CNS abscesses and post-neurosurgical infection, where treatment options and efficacy are significantly limited by the low glycopeptide transfer, and the spread of glycopeptide-resistant bacterial strains. When severe CNS infections are of concern, linezolid is a safe and effective choice for the management of ascertained or highly suspected infections caused by gram-positive cocci. Novel therapeutic scenarios are therefore opened for the clinicians, given that a selective administration is carried out, in order to save the high drug potential, and limit the spread of microbial resistance.

PP 6.14

Cat-Scratch Disease as an Emerging Illness in both Children and Adults: clinical presentation and management perspectives

Manfredi R, Sabbatani S, Chiodo F. Infectious Diseases, University of Bologna, Italy

The spectrum of human disease caused by *Bartonella* spp. has expanded rapidly over the past 2 decades, prompted by the association of cat-scratch disease (CSD), AIDS-related bacillary angiomatosis, and bacillary peliosis, with the fastidious gram-negative bacillus formerly identified as *Rochalimaea henselae*, and later classified in the genus *Bartonella*. CSD warrants extensive investigation, from an epidemiologic, diagnostic, but especially therapeutic point of view. Two suggestive episodes of *Bartonella henselae*-caused CSD are reported. The first case occurred in a 60-year-old man, thus suggesting to maintain an elevated suspicion for this disease also in adults. Both episodes were characterized by a very prolonged and complicated disease course (with the involvement of 3 lymph node sets in the first case), evolved into or needed lymph node drainage, and showed an apparently negligible activity of many antimicrobial courses, with a very low tendency to local cure despite repeated medications. While specific culture and molecular biology techniques proved negative (probably due to the late availability of appropriate clinical specimens), indirect immunofluorescence assays proved positive since the first weeks of disease, and elevated levels were recognized also many months after disease onset. Despite multiple chemotherapy attempts carried out with ceftriaxone, co-amoxycylav, levofloxacin, tetracyclines, spontaneous fistulization of right epitroclear lymph nodes occurred in the adult patient, while amoxycillin, ceftriaxone, azithromycin, cotrimoxazole, and co-amoxycylav use did not prevent a similar clinical course in the 9-year-old boy, who suffered from severe axillary lymph node localization. Two case reports of CSD with distinguishing features, characterized by adult onset in the first patient, and a very long course accompanied by persistently positive serologic assays occurring in both episodes, are described, also in relation with need and eventual selection of antimicrobial treatment. Although CSD is usually a self-limiting disorder within a few weeks or months, a locally severe disorder or a disseminated illness may occur. When clinicians face patients with a prominent swelling of lymph nodes draining from the upper limbs, CSD may be suspected on the ground of epidemiological-clinical features, and a limited systemic involvement contrasting with a prominent local disease. The significance of specific antibody temporal kinetics in relation with the subacute disease course is still unknown. Although biomolecular assays are now available, the time elapsed from disease onset to clinical diagnosis usually hampers positive results, while the role of surgical debridement and that of the unpredictable activity of antimicrobial chemotherapy warrant careful investigation. In fact, the chemotherapy of CSD is still strongly discussed, as to need, selection, and duration of treatment. While some authors claim that no controlled evidence is available to determine its definitive benefit, other investigations tend to attribute a significant role to a broad spectrum of antibiotics. Actually, the majority of *Bartonella* spp. isolates appear susceptible in vitro to a wide range of beta-lactams, as well as rifampicin, erythromycin, and tetracyclines, while sensitivity to clindamycin, quinolones, and cotrimoxazole seems more variable. A remarkable discordance between in vitro and in vivo activity of several molecules has been also found.

PP 6.15. Diarrhea Caused by New Organisms

Kwaabena Appau G, Kofi Owusu K.
Institute of Advanced Technology, Kumasi, Ghana

Discovery of new diarrheal pathogens, as with any other infectious illness, requires proof of disease causation. This becomes an awesome task if the putative organism cannot be cultured and an appropriate disease model is not established. Currently available diagnostic methods rely heavily upon culture and are, therefore, inadequate. Meticulous clinical observation and epidemiologic analyses complemented by genotypic approaches including PCR should be utilized to identify hitherto unrecognized diarrhea pathogens.

About 50 different pathogens are known to cause diarrheal disease and half of them were described in the last 3 decades. In 1992 a new serotype, *Vibrio cholerae* 0139, was identified to be responsible for an outbreak of cholera in India. First reported from North America in the '80s, outbreaks of *Escherichia coli* 0157 hemorrhagic colitis have been reported recently from Japan, the Central African Republic and Cameroon. One of the most dreadful complications of *E. coli* 0157 infection is hemolytic uremic syndrome (HUS).

The protozoa *Cryptosporidium parvum* and *Cyclospora cayetanensis* have assumed significant etiologic roles in diarrhea among AIDS patients. *C. parvum* is an important cause of protracted diarrhea in both immunocompetent and immunocompromised patients. First described in 1993, *C. cayetanensis* causes both protracted and recurrent diarrhea in general, and more severe disease in AIDS patients. As with other diarrheal diseases, rehydration and nutritional support are the key elements in the management of diarrhea due to these new pathogens.

Antibiotic treatment in *E. coli* 0157 infection should preferably be avoided as it can precipitate HUS. There is no effective treatment for cryptosporidiosis, although paromomycin and nitazoxanide have been found to be beneficial. Cyclosporiasis can be treated with co-trimoxazole.

PP 6.16.

The Evaluation of Antibacterial Pattern of Nosocomial Pathogens Isolated in Iran

Khorshidi A, Sharif A, Moosavi GH.

Kashan University of Medical Sciences, Kashan, Iran

Background: Nowadays nosocomial infection and antimicrobial agents against nosocomial pathogens are one of the most important health problems in the world. **Objective:** Regarding to the high prevalence of nosocomial infection in Intensive care (ICU) in Shahid Beheshti Hospital of Kashan (Iran), this study was designed in during (June 2002 to May 2003).

Material and Methods: A descriptive study was performed over existing data of gram negative cultures in patients that were hospitalized more than 48 hours the demographic characteristic were registered, then the results of research were presented descriptive analysis.

Results: Among 58 patients under the study, 91 cases were positive cultures of gram-negative bacteria that 79.3% belonged to males and 20.7% to females. The most frequent infection was showed in males under 30 ages, the most frequent infection was showed in ICU ward (68.1%) and the most common infection site was respiratory system (32.9%) and the most common pathogen belonged to Klebsiella (39.5%) that showed the most sensitivity against to Ciprofloxacin, third generation Cephalosporines (Ceftazidim), The most resistant against to Cephaloxin, Cephatolin (First generation Cephalosporins).

Conclusion: Regarding to the high prevalence of nosocomial infection and increasing of antibiotic resistance particularly in ICU ward with respiratory system infection, it's necessary to consider the predisposing factors of nosocomial infection in ICU and regarding improved attention to hygienic principles, it's suggested to organize an infection central committee in this center and recommended notice and necessary in the selecting of choice drug particularly use of third generation of Cephalosporins.

Keyword: Antibacterial pattern, Nosocomial Infection

PP 6.17.**Evaluation of Acute Bacterial Sinusitis Etiology and Determination of Antibiotic Sensivity in Iran**

Khorshidi A, Yeganeh Moghaddam A, Sokoot A, Moosavi GH.
Kashan University of Medical Sciences, Kashan, Iran

Background: Acute bacterial rhinosinusitis is a common respiratory infection of children, and its management is made more difficult by the lack of definitive diagnostic criteria that precisely established the diagnosis.

Objective: Regarding to the problems of patients with acute sinusitis and inefficacy of common and current drugs in treatment. This study was conducted in Kashan (Iran) during (Sep 2001 to Jul 2003).
Material and Methods: A Descriptive study was performed over 43 patients with acute sinusitis that referred to the Central Laboratory of Kashan University in during 2002 & 2003, all of patients were examined by otolaryngologist, then referred to central laboratory, the questionnaire by containing questions and characteristics demographic, symptoms, used drugs, were completed. The specimens were collected by strill swab from nasopharyngial and nasal secretions, then were cultured on the media: Blood agar, Eosin Methylen Blue (EMB), thioglycolate, isolated specimens were identified by National Committee for Central Laboratory (NCCL). Antibiotic susceptibility was determined accordance disk diffusion method (Kirby & bauer), the results of research were presented by descriptive analysis.

Results: Research showed: The most common age in acute bacterial sinusitis was in the range of 20-29 years (46.5%), the most common symptoms was determined frontal pain, or headache (83.7%), the most common organism in nasopharyngial secretion was determined *Streptococcus pneumonia* (52.2%), and nasal secretion *staphylococcus aureus* (53.5%). The most rate of antibiotic sensitivity was Ciprofloxacin and Erythromycin, Cephazolin and third generation of Cephalosporins (Ceftriaxon).

Conclusion: Althoght, nowadays current antibiotics such as: Co-Amoxiclav, Co-trimaxazal and Ampicillin were used, but repeated reinfections in the patients were observed, therefore it seems the process of treatment is necessary to be changed. We suggest susceptibility test can help to clinician in treatment. A reasonable use of clinical symptoms and paraclinical and treatment with combined drugs can be effective to prevalent the recurrent sinusitis.

Key word: Acute sinusitis bacterial, Antibiotic Sensivities

PP 6.18

Clinical Finding in Patient Presenting with Sore Throat.

Khorshidi A, Taghaddosi M, Nadi Ravandi M, Hosseini nejad A, Khorshidi S. Kashan University of Medical Sciences, Kashan, Iran

Objective: The aim of this research was to determine the prevalence of streptococcal pharyngitis (group A- beta hemolytic streptococci) among patients suffering from tonsilopharyngitis and to identify clinical criteria predicting GA β HS pharyngitis.

Material: A cross β sectional study was conducted over 400 Patients with acute pharyngitis who were referred to clinic of Kashan Medical University in IRAN period (November 1997 to January 1998). Demographic data and signs for each patient were recorded on a Standardization Form and a throat Swab was taken using the filter paper Technique, then the samples was cultured according Standard Methods (NCCLS), The results of research were presented by descriptive analysis. (Chi-Square and fisher β s exact test).

Methods: The rate of prevalence of GA β HS was 8.5% and the highest isolation was reported in children aged 10-15 (64.7%), Non-GA β HS in cluded 76.5% of total isolation. The most prevalence of GA β HS was in winter and early spring, significant predictors of GA β HS pharyngitis Clinicl signs were: Sever pharyngeal erythema 26 (76.6%), ($P < 0.100000$), Fever 29 (85.3%) and ($P < 0.0001482$) and Petechia 6 (17.6), ($P < 0.0000061$) and Tenderness of lyphnodse 14(41.2%), ($P < 0.000001$) and Pharyngeal excudate 12 (35.3%), ($P < 0.0003888$) and Enlargment of lyphnodse 14 (41.2%), ($P < 0.0000247$). Antibiotic Sensivity test showed higher sensivity to Cephalosporin, Ampicillin, and Erythromycin.

Conclusions: Results suggest that a syndrome of signs could be used as a clinical prediction for the diagnosis of GA β HS pharyngitis.

Keywords: Pharyngitis, GA β HS, Clinical Finding

PP 6.19.**Prevalence of *Neisseria gonorrhoeae* in Cervicitis and Evaluation of Drug Resistance of *Neisseria gonorrhoeae* in Kashan-Iran**

Tabassi A, Khorshidi A, Alinaghi N.

Kashan University of Medical Sciences, Kashan, Iran

Background: Due to the relatively high prevalence of cervicitis and its complications such as pelvic inflammatory diseases that may lead to infertility, the present study was designed in order to determine the prevalence of gonococcal cervicitis and drug resistance of those in kashan in 2001.

Material & Methods: A descriptive study was carried out on patients with cervicitis referring to gynecology clinics. After physical examination and diagnosis of cervicitis, the sample collected from endocervix. The specimens were cultured on Thayer-Martin agar plates. After identification of isolated gonococci by standard methods: National Committee Control Laboratory (NCCL). Susceptibility tests were performed to determine the sensitivity or resistance of gonococci to common antibiotic; the data were presented using descriptive statistical analysis.

Results: Of 315 women patients with cervicitis. 2 (0.63%) had gonococcal cervicitis, was of whom were under 25 years old. The age at which sexual activity started was $\bar{A}\bar{A}$ 20 years and they have both frequency and dysuria. One of them had revealed resistance to Vancomycin and the other had resistance to Ceftriaxon.

Conclusion: Due to the relatively high prevalence of gonococcal cervicitis in western country, the prevalence of 0.63% in this study is not hazardous. Meanwhile, gonococci in this area are sensitive to common antibiotics

PP 6.20.

Embryonic Hematopoietic Stem Cells in Chronic Active Hepatitis

Smikodub OI.

Cell Therapy Clinic of National Medical University and Embryonic Tissues Center EmCell, Kiev, Ukraine

Observed were 8 patients with chronic active hepatitis, duration of the disease being 6-23 months. In all patients, the process was estimated as active, in 3 patients it was expressed, in 5 - moderate. Hepatitis B markers were found in the serum of 2 patients (HbsAg, anti-HBc, HbcAg); there were no antibodies to smooth musculature, immunoregulating index was also reduced (1.2 - 0.8) secondary to decreased CD4+ count. The above taken into consideration, 6 patients were described as having autoimmune hepatitis, and 2 - chronic active hepatitis. All patients reported loss of weight (7-12% lower than the norm), expressed weakness, low appetite, jaundice, subfebrile fever, itching. 2 patients had vasculitis rash. In 1 case, hepatitis was combined with non-specific ulcerative colitis (expressed reaction to smooth musculature antibodies).

3 patients presented systemic osteoporosis, calcinosis of large arteries, cartilages, stones. All patients were noted to have hepatomegalia: in 1 case there was a combination of hepatomegalia and spleenomegalia with hypersplenism (anemia, thrombocytopenia). 4 patients had expressed asthenoneurotic syndrome, others - somatogenic depression. Hematopoietic embryonic stem cells (HESC) were obtained from liver, spleen, and bone marrow of 4-8 weeks old embryonic cadavers.

After HESC transplantation, all patients reported syndrome of early post-transplantation improvements and syndrome of psychofunctional changes. In 8-12 hours, patients already felt improvement of general condition, decrease of weakness and sweating, temperature drop, improvement of the appetite. Many patients also reported improvement of sleep and normalization of its formula. As for psycho-functional status, it is necessary to note the following: improvement of general emotional state, decrease of alertness and anxiety, growing faith in recovery. Clinical manifestations of these syndromes were expressed during the first month of post-transplantation period. Within two weeks, there was a considerable increase of CD3+, CD4+, CD8+, CD19+ counts; immunoregulation index decreased. Concentration of bilirubin in the blood was also reduced. This resulted in the increase of ferment activity, which indicates activation of cytolysis in liver cells. This process was well maintained within first 2-3 weeks, by 4-5 week, as a rule, there appeared a tendency for the decrease of transferase activity. Clinical manifestations of jaundice, choleamia and intoxication decreased and disappeared at the end of 1-2 months after transplantation. In the future, parameter changes of inflammatory process activity and liver cell insufficiency had wave-like pattern and were characterized by minimal activity. Remission achieved lasted for 4.3 ± 0.5 years.

PP 6.21.**Significantly Increased Frequency of Hepatitis A in a Metropolitan Area of Northern Italy. Need of counselling and prophylactic measures for male homo-bisexual population**

Manfredi R, Sabbatani S, Frank G, Chiodo F.

Infectious Diseases, University of Bologna, and Department of Neurosurgery, Bellaria Hospital, Bologna, Italy

Aim of our study is to realized an observational survey of all hospitalizations due to a diagnosis of acute hepatitis A, carried out in the Bologna metropolitan area (where around 500,000 people live or study), 1999 to April 17, 2004. At our inpatient centre of Infectious Disease are referred all patients with suspected and/or confirmed hepatitis A for needed oral-fecal isolation measures: 122 consecutive patients were hospitalized in the examined 5-year, 4-month period. Since October 2002, hospitalized acute hepatitis A largely prevailed over acute HBV and HCV hepatitis, and became the most frequently recognized acute hepatitis among our inpatients. Although a modest seasonal prevalence remained, as expressed by the notification of 70 out of 122 cases in the period ranging from April to September (57.4%), compared with October to March (42.6%), other analyzed demographic and epidemiological features gave a signal of a rapidly changing epidemiology of this disease, despite the introduction of a specific anti-HAV immunoprophylaxis since the year 1995. Adult female patients and children-adolescents (aged from 4 to 9 years), represented only 18 cumulative patients out of 122 (14.8%), with a temporal trend of diagnosis which remained substantially unchanged through time. Among the 122 overall patients, the prevalence of immigrated subjects recently increased, from 1-3 cases per year from 1999 to 2001, up to 12 cases in the 16 months from January 2002 to April 17, 2003 ($p=.036$). Two couple of young foreign siblings (aged 6-8 years) were hospitalized in the year 2002. When focusing on the great majority of patients with a newly diagnosis of hepatitis A, we have to underline that even 104 out of 122 cases (85.2%) were represented by male young adults and adults, with an age ranging from 22 to 44 years (mean 28.3 ± 4.3 years). When exploring clinical history for possible risk factors for hepatitis A in this last patient population of 104 adult male subjects, consumption of possibly contaminated food was reported by 19 patients only (18.3%), but 72 of them (69.2%) recognized unprotected homo-bisexuals contacts in the two months preceding the onset of hepatitis A, and in the remaning 13 cases (12.5%) epidemiological search was incomplete or not exhaustive. Surprisingly, nobody reported contacts with patients with a recently diagnosed hepatitis A, and nobody underwent prior specific anti-HAV vaccination. Concurrent infectious disorders included previous or present hepatitis B in 16 cases, hepatitis C in 9, syphilis in 5, and HIV in 11 patients (with HIV infection disclosed concurrently with hepatitis A in two cases of ours). The temporal trend of young men and adults admitted for hepatitis A showed an significantly increased absolute number from 1999 to the first four months of 2003: 14 cases diagnosed in the year 1999, 13 patients in the year 2000, 18 cases the year 2001, 23 in the year 2002, 38 cases in the year 2003, and 12 in the first 108 days of year 2004. Although hepatitis A is usually characterized by a proportionally benign course and absent risk of chronicization, however the rapid spread of this disease despite the availability of anti-HAV vaccination clearly recognized an increased prevalence of homo-bisexual transmission over other oral-fecal routes of transmission, as already noticed in the United States in the late nineties (MMWR 1998; 47:708-10). A careful epidemiological monitoring, specifically targeted informational and educational campaigns, and public health measures (such as an extensive recommendation of immunoprophylaxis for patients with at risk behaviors), are expected to contain the present outbreak of hepatitis A among homo-bisexual men, and concurrently reduce the spread of other potentially sexually-transmitted diseases, such as hepatitis B and C, HIV, and syphilis.

PP 6.22.

A Standardized Infectious Disease Screening of Patients Undergoing Orthotopic Liver Transplantation

Manfredi R, Sabbatani S, Frank G, Chiodo F.

Infectious Diseases, University of Bologna, and Department of Neurosurgery, Bellaria Hospital, Bologna, Italy

Patients with end-organ liver disease who are candidate to an orthotopic liver transplantation undergo an extensive and standardized infectious disease screening during the weeks which precede the introduction in the transplantation list and eventual surgery. This assessment is aimed at excluding active or latent infections, which could be responsible for short- and mid-term infectious complications. Since 33 months, the outpatient service of our Division is engaged in a systematic infectious disease assessment of all patients listed for orthotopic liver transplantation. The first-line evaluation includes serologic testing for HIV-1 and HIV-2, syphilis, *Toxoplasma gondii*, Cytomegalovirus, Herpes simplex Virus, Varicella-zoster virus, Parvovirus B19, and hepatitis A, B, C, and D (HAV, HBV, HDV and HCV), while microscopic and culture examination for the search of bacteria, mycobacteria, fungi, and parasites are performed on sputum, urine, nasal, pharyngeal and vaginal swab, and stools. A Mantoux intradermal reaction is carried out and checked within 72 hours; assessment for a suspected tuberculosis is eventually completed with chest X-ray, high-resolution thoracic tomography, and/or bronchoscopy and bronchoalveolar lavage). Should a tubercular disease be of concern, subsequent chemoprophylactic and therapeutic interventions are required, as appropriate). The eventual microscopic and culture positivity is carefully evaluated, in order to distinguish between colonization and infection, and to suggest an eventual chemotherapy and/or repeated microbiological examinations. Individualized active immunoprophylaxis schedules (vaccine administration for pneumococci, Influenza, HAV and HBV hepatitis), are finally recommended as a part of a comprehensive infectious disease assessment. In the 33-month considered period (starting from January 2001), 391 consecutive patients have been examined (288 of them were males). The predominant underlying disorders were HCV-related liver cirrhosis, followed by HBV-associated hepatic cirrhosis, alcoholic liver cirrhosis, and more infrequently autoimmune, cryptogenetic, and primary biliary cirrhosis. All assessed patients underwent at least one infectious disease assessment, whose figures have been stored in a dedicated electronic database, in order to allow eventual correlations between demographical, epidemiological, clinical, microbiological, laboratory, and instrumental variables of all patients waiting for liver organ transplantation. Because of the emerging of a broad spectrum of problems and concern strictly depending on diseases of the immunocompromised host at risk for opportunism due to underlying diseases, both primary or secondary immunodeficiency, and solid organ transplantations per se, the role of Infectious Disease consultant has an extensive spectrum of problems to be considered, from recommendations regarding anti-infective chemoprophylaxis, to diagnosis and treatment of opportunistic complications related to solid organ transplantation and related iatrogenic immunosuppression. The Infectious Disease consultant is also called to give a crucial contribution in terms of screening of patients listed for transplantation, and prevention of the most common infectious complications, which pose transplant recipients at risk for organ rejection, and local or systemic opportunistic diseases, encompassing a viral, bacterial, fungal, or infrequently parasite origin.

PP 6.23. **Myxobolus sp., a Possible New Opportunistic Parasite in Immunocompromized Patients**

Hessen EM, Zamzame ML. Faculty of Medicine, Suez Canal University, Ismailia, Egypt

During a study on intestinal parasitic infections in immunocompromised patients complaining of diarrhea, a parasite belonging to the phylum Myxozoa recently described from human samples was identified in three stool samples out of eleven. When this parasite was stained with modified Ziehl-Neelsen staining method the features of the spores were identified: they were pyriform in shape with an average size 14.0 μ in length and 10.0 μ l in width. Every spore has thick wall and one suture in the anterior third followed by two polar capsules. Each polar capsule has about four to five coils ending by polar filaments at the suture level. The size of the polar capsule is 2.5x 3.5 μ . Co-infection with *Cryptosporidium parvum* parasite was also found in the first sample and *Giardia lamblia* cysts were found in the second sample and *Hymenolepis nana* eggs were detected in the third sample. Given that the three patients were also infected with other pathogens that cause diarrhea, so the pathogenic role of this parasite and route of infection could not be established.

PP 6.24.
Helicobacter pylori Infection in Children: utility of culture in diagnosis and to study the antimicrobial susceptibility

Sabbi T, Argentieri M, Menichella D, De Angelis P, Torroni F, Federici di Abriola G, Colistro F, Dall'Oglio L.
Pediatric Unit Belcolle Hospital, Viterbo; Microbiology Department, Digestive Surgery and Endoscopic Unit, Biochemistry Bambino Gesù Pediatric Hospital, Rome

Background. *Helicobacter pylori* (Hp) causes one of the most widespread infections worldwide: it affects more than 50% of the human population and the acquisition of infection occurs during infancy. Hp infection has been recognized as a cause of chronic gastritis, peptic ulcer, atrophic gastritis and, also, gastric cancer. This infection can be diagnosed by invasive techniques requiring endoscopy and biopsy (histological examination, rapid urease test, culture) and by non invasive tests (serology, urea breath test, detection of Hp antigen stool specimen). The eradication therapy implies an association of a proton pump inhibitor (PPI) and two antibiotics (mainly nitromidazoles, macrolides and beta-lactames). The bacterial resistance to antibiotics more frequently used represents one of the most important factors of treatment failure.

Aims. To determine the accuracy of culture for diagnosis of Hp infection and to evaluate the prevalence of resistance to amoxicillin, metronidazole and clarithromycin in isolates of Hp in children. Methods. 80 biopsies gastric were obtained from paediatric patients (50 Male; age range 3-18 years; mean age 9 years) and processed for histology examination, rapid urease test, culture. 80 faecal specimens were processed for detection of Hp antigen stool. All positive cultures were tested for antimicrobial susceptibility by E-test for amoxicillin, metronidazole and clarithromycin.

Results. The results (%) of diagnostics methods are reported in the table.

Test	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)
Histology	100	100	100	100
Culture	92	100	100	96,5
Rapid urease test	72	96,3	90	88,3
Stool test	56	87,3	66,7	81,3

· Positive and negative predictive value

The E-test in-vitro antimicrobial susceptibility testing showed that 26% of the isolates were resistant to clarithromycin and 30% to metronidazole. No resistance to amoxicillina was observed. Conclusions. Microbiological isolation of Hp is important to determine the resistance status and the evaluation of antibiotic resistance profiles from paediatric patients can help in optimising therapeutic regimen to prevent treatment failures.

PP 6.25.**Incidence Of Chlamydia Trachomatis In Genital Infections**

Kovov D, Kovova N, Parmuzina R.

Vitebsk State Medical University, Vitebsk, Belarus

Introduction: Chlamydia trachomatis is the most commonly reported infectious disease in the industrialized countries. Every year reported about 68 millions cases throughout the world. Early identification through annual screening and appropriate treatment can significantly reduce the short- and long-term complications. In men, Chlamydia trachomatis is the commonest cause of non-gonococcal or (less correctly) non-specific urethritis. In women, the organism may infect both the cervix and the urethra. Epididymitis may complicate infection in men, whilst in women infection in the upper genital tract - the endometrium and the fallopian tubes, may lead to acute pelvic inflammatory disease (PID). Rate of chlamydial infection increases every year in spite of all measures provided by physicians. The aim of study was to obtain data on incidence of Chlamydia trachomatis in samples taken from genital tracts in men in 2003 year.

Methods: A total of 3960 urethral (men) swabs were analyzed at the Vitebsk State Medical University. The diagnosis was made with the method of direct immunofluorescence (Chlamydia Direct IF identification-bioMerieux, France).

Results: Of a total 3960 samples analyzed in this period, 1247 samples were positive for Chlamydia trachomatis, it was 31.48% . We analyzed all infected men upon age, place of living, methods of contraception, number of sexual partners in the recent years. There is a significant connection between subjective ailments such as: urethral discharge, dysuria. Asymptomatic in up to 50%.

Discussion: The percentage of detection of Chlamydia trachomatis, approximately every third patient, has proved that this bacterium has the leading part in the etiology of sexually transmitted infections in Belarus. This urges the need of cost-effective screening procedures and appropriate treatment followed after sensitive and specific diagnostic procedures in Belarus. To prevent repeat infections, partners must be provided timely and appropriate antibiotic treatment.

PP 6.26. Purification Of Trichomonad DNase By DNA-cellulose Affinity Chromatography

Mathur HSS, Perry D, Greenwell P. University of Westminster, London, UK

Trichomoniasis has been associated with vaginitis, cervicitis, urethritis, pelvic inflammatory disease (PID), and adverse birth outcomes. Infection with *T. vaginalis* could have an important role in transmission and acquisition of HIV. Trichomonads are completely reliant on their hosts for sugars and nucleotides and hence produce and secrete large amounts of specialised glycosidases and Deoxyribonucleases. Analysis of the proteins and genes may allow us to formulate new treatments for the disease based on either enzyme inhibition or anti-sense gene therapy: such strategies have been used on other genital disorders e.g. Herpes simplex virus.

Affinity chromatography was used to purify the DNases secreted by the organisms. To date, there is no work published on this enzyme from the Trichomonads. Calf thymus DNA was used as an affinity ligand on a cellulose solid support within the column. The enzyme purified was then used for further analysis. Crude enzyme extract was precipitated in 80% saturated ammonium sulphate at 4 °C. The resultant precipitate was dialysed against water overnight at 4 °C, and used as a raw material for SDS-PAGE analysis and DNA-cellulose affinity chromatography. The purification achieved was 15 fold. The SDS-PAGE analysis of the active fractions demonstrated the presence of three protein species of size: 40 kDa, 30 kDa and 25 kDa. Isoelectric focusing produced one band of pI 6.8. This suggests that either the protein is multimeric with 3 subunits or that there are different glycoforms with identical pI.

Scale up of this method should allow purification of DNase in quantities suitable for sequence analysis and identification utilising bioinformatics resources.

PP 6.27.**Molecular Characterisation of Enterotoxigenic *Escherichia coli* Isolates from Children with Diarrhoea**

Jafari A, Bouzari S.

Pasteur Institute of Iran, Tehran, Iran

Enterotoxigenic *Escherichia coli* (ETEC) is a leading cause of infantile diarrhea in developing countries as well as an important etiologic agent of traveler's diarrhea. ETEC strains are identified by the ability to produce enterotoxin, either heat-labile (LT) or heat-stable (ST) toxin or both. A total of 619 *E. coli* isolates from diarrheal cases were tested for the presence of LT and ST genes using DNA hybridization technique. The probes used for these toxins were excised by *HincII* enzyme from pCVD403 and *EcoRI* from pCVD427 respectively. The resulting fragments of 1200bp for LT and 216bp for ST were DIG-labeled using random hexameres and Dot-blot hybridization was performed under stringent conditions. The results obtained showed that 60 (22.7%) isolates contained only LT, 106(40%) only ST and 98(37.2%) both LT and ST coding genes. The remaining isolates were probe negative. Resistance to 9 commonly used antibiotics was also tested by disk diffusion method in 246 of the probe-positive isolates, of which only 38(15.4%) were sensitive to all the antibiotics used and 163(78.36%) carried resistance markers to more than one antibiotic. The highest rate of resistance was against sulfamethaxazole-trimethoprim alone or in combination with other antibiotics and the least resistance was observed against cefalotin and Nalidixic Acid respectively. Presence of integron class 1 in 27 resistant isolates was determined using PCR and was observed in 88.8% (24/27) of the isolates. In conclusion, the results of this study indicates frequent presence of enterotoxin genes and antimicrobial resistance phenotypes among our isolates.

SL 1.2. New Concepts & Anti-HIV Therapy"

Robert C. Gallo, MD

Director

Institute of Human Virology

University of Maryland Biotechnology Institute

University of Maryland Baltimore

As new approaches to HIV therapy we are focused on (a) CCR5 entry inhibitors and (b) on interference with HIV induced cytokine dysregulation.

(a) With CCR5 inhibitors we (A. DeVico and T. Fouts) have developed an immunoadhesin which binds CCR5 and prevents HIV co-receptor interactions. This inhibitor is composed of the gp120 binding region of CD4 and the consequent conformationally altered gp120. An Ig H chain hinge region was joined to the complex for stabilizing the molecule. Inhibition of R5 HIV is equal to or greater than various potent monoclonal antibodies which block HIV entry. Also, we (R. Redfield and A. Heredia) are studying cytostatic agents which stimulate the production of β -chemokine CCR5 ligands and diminish expression of CCR5. These agents (e.g. rapamycin) markedly enhance the activity of drugs which directly target CCR5.

(b) HIV pathogenesis is associated with rising levels of IFN- α ; partly from Tat stimulation of IFN- α production from APCs. In collaboration with D. Zagury (Paris) and F. Romero in our group, has shown that IFN- α promotes T-cell immune suppression by promoting formation of Tr cells. We think the accumulation and systemic distribution of these Tr cells may be a key part of the indirect effects of HIV on uninfected cells, a major aspect of HIV pathogenesis. Clinical studies with A. Gringeri (Milan) and P. Hermanns (Brussels) with a small (31) number of patients suggests that targeting IFN- α (as well as Tat) with therapeutic vaccines is safe and may be efficacious, but conclusive results will require larger trials.

WS 1.1.

PI Cross-Resistance

Bernard Masquelier (1), François Raffi (2)

(1)Département de Virologie et Immunologie, CHU de Bordeaux; (2) Département des Maladies Infectieuses, CHU de Nantes, France

Protease inhibitors (PI) resistance usually require accumulation of resistance, with medium to high-level cross-resistance according to the different compounds. PI - cross-resistance has become a problem of increasing importance in the therapeutic management of antiretroviral-experienced, HIV-infected patients. The mechanisms leading to the accumulation of PI resistance mutations will be described; the molecular epidemiology and the increase of resistance over time will also be discussed. The validation of interpretation algorithms for genotypic resistance assays is a key point in order to optimize the salvage therapy regimens; several examples of algorithms for PI will be presented. Pharmacokinetic boosting of PIs by low dose ritonavir provide numerous advantages among which overcoming decreased susceptibility of mutated viruses. Indeed, for the most recent available boosted PIs, i.e. fosamprenavir/r and lopinavir/r, available clinical data demonstrate antiviral response to regimens including these drugs even for viruses with up to 5-6 primary PI mutations. In the setting of multi-resistance to the whole PI class, the use of newer drugs with potential activity on resistant isolates can also overcome the cross-resistance. Tipranavir/ritonavir is associated with retained activity against multiple-resistance viruses and demonstrate significant antiviral responses in cases where other boosted PIs are ineffective. Antiviral activity of tipranavir according to the mutational patterns will be discussed.

WS 1.2. Tipranavir:2004 Update

Laurence WEISS, Department of Immunology, Hôpital Européen Georges Pompidou, Paris, France

TPV, the first non-peptidic protease inhibitor has been assessed first in patients who have failed a previous PI containing regimen and is currently in phase III clinical development. In vitro, TPV activity against clinical strains of HIV resistant to 3 or more PIs has been well established. In vivo, tipranavir must be administered twice daily in combination with low doses of ritonavir in order to increase the drug bioavailability and reach a C_{min} higher than the protein-adjusted IC₅₀ for most PI resistant viruses. Results from a recent phase II, dose ranging, comparative study (1182.52) have shown that the 500/200 tipranavir/ritonavir dose was the best compromise, taking into account pharmacokinetics, toxicity and activity data. The virologic activity of tipranavir was better against viruses exhibited ≥ 2 mutations: at codons 33, 82, 84 and 90 in the protease gene.

Patients who were not eligible to RESIST phase III program due to a genotypic exclusion criteria (patients with more than 2 mutations at codons 33, 82, 84 and 90) were proposed to participate to a phase II, 24 weeks, open label, safety and pharmacokinetic study of TPV/r alone or in combination with a second boosted PI. These patients were randomized in one of the following four arms: TPV/r (500/200) control arm, TPV/SQV/r (500/1000/200), TPV/APV/r (500/600/200) or TPV/LPV/r (500/400/200). The interim analysis demonstrated the short term safety of TPV/r alone or in combination with APV, LPV or SQV. Reductions in plasma PK parameters of SQV, LPV and APV were observed when co administered with TPV/r. The week 4 viral load reductions were similar for both TPV/r control arm and the other dual boosted PI arms so that the clinical relevance remains unknown at this time. The use of dual boosted PI regimens including tipranavir requires a careful pharmacological monitoring.

In addition to a better identification of the tolerance and toxicity profile of TPV/r, the currently on going program (RESIST studies) will help to identify the type of patients who will benefit most from tipranavir. The two pivotal trials (RESIST 1: BI 1182.12 and RESIST 2: BI 1182.48) are studying more than 1500 treatment-experienced HIV+ adults in over 20 countries and 3 continents. Both RESIST 1 and 2, enrolled patients presenting less or 2 mutations at codons 33, 82, 84 and 90 on the protease gene and previously treated with at least 2 PI containing regimen. Both trials were fully enrolled during 2003 and 24 week data will become available for analysis in the Spring of 2004.

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& les Maladies Infectieuses Emergentes.*

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Additional information about Abbott and virology

Abbott Laboratories has been a leader in HIV/AIDS research since the early years of the epidemic. In 1985, the company developed the first licensed test to detect HIV antibodies in the blood, and remains a leader in HIV diagnostics. Today, Abbott retroviral and hepatitis tests are used to screen more than half of the world's donated blood supply. To treat those with HIV, Abbott scientists have developed two protease inhibitors.

ABBOTT France est une filiale d'Abbott Laboratories, groupe international de premier plan dans le domaine de la santé, qui se consacre à la recherche, au développement, à la fabrication et à la commercialisation de médicaments, de produits de nutrition médicale, de produits hospitaliers, ainsi que des instruments et dispositifs de diagnostic.

Environ 60 000 personnes dans le monde travaillent à mettre à la disposition des patients des produits d'avant-garde qui influent grandement sur la pratique médicale et la qualité des soins. Son siège social étant situé dans la banlieue nord de Chicago, Abbott Laboratories commercialise ses produits dans plus de 130 pays. En 2003, son chiffre d'affaire mondial s'élève à 19,6 \$ US.

Informations supplémentaires à propos d'Abbott et de son implication dans le domaine de la virologie

Abbott Laboratories est un des leaders dans le domaine de la recherche VIH/SIDA depuis les premières années de l'épidémie. En 1985, la compagnie lance le premier test de dépistage des anticorps du VIH dans le sang, et elle demeure aujourd'hui un référent dans le diagnostic du VIH. Les tests virologiques Abbott sont utilisés pour tester plus de la moitié du sang utilisé en transfusion dans le monde. Par ailleurs, afin de traiter les patients séropositifs, les scientifiques d'Abbott ont développé deux inhibiteurs de protéase.

BAYER HEALTHCARE - DIVISION DIAGNOSTICS

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With approximately 7,000 employees worldwide and 2002 sales of \$1.9 billion, Bayer Diagnostics (www.bayerdiag.com), based in Tarrytown, New York, U.S.A., is one of the largest diagnostic businesses in the world.

The organization supports customers in 100 countries through an extensive portfolio of central, self-testing, nucleic acid (Versant® and TRUGENE® product lines for the qualitative and quantitative detection, and sequencing of HIV, HCV, and HBV viruses) and near patient care diagnostics systems and services for use in the assessment and management of health, including the areas of cardiovascular and kidney disease, oncology, virology, women's health and diabetes.

A propos de Bayer Diagnostics

Avec près de 7000 collaborateurs, un CA en 2002 de 1.9 milliards de dollars, Bayer Diagnostics, basé à Tarrytown, NY, USA, figure parmi les premières sociétés mondiales dans le secteur du diagnostic.

Présente dans 100 pays, ses activités s'articulent et se développent dans les laboratoires d'analyses, les hôpitaux et chez les professionnels de la santé, autour des systèmes d'auto surveillance, de biologie moléculaire (gammes Versant® et Trugene® pour la recherche qualitative et quantitative des virus VHC, VHB et VIH et leur séquençage).

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The long-term development of new antiretroviral therapies, all aimed at extending and improving quality of life for people with HIV/AIDS, has become a major part of Bristol-Myers Squibb worldwide research efforts.

The Company has a promising pipeline including recently bringing to market the first once-daily protease inhibitor.

The Company continues work to improve upon and advance existing drug formulations. BMS is the first pharmaceutical company to offer once-daily medications in all three orally administered antiretroviral classes, providing the building blocks for once daily regimens across multiple lines of therapy.

Bristol-Myers Squibb a été l'un des premiers laboratoires à s'engager dans la lutte contre le SIDA. Dès 1984, ses équipes de recherche ont commencé à travailler sur le développement d'antirétroviraux. Depuis près de vingt ans, Bristol-Myers Squibb, s'investit non seulement dans la recherche de thérapeutiques efficaces, mais aussi dans tous les domaines qui concourent à combattre le VIH : prévention, information et formation, aide aux associations, accès aux soins et lutte contre la pandémie de SIDA en Afrique.

Cet engagement a notamment conduit Bristol-Myers Squibb à mettre à la disposition des patients VIH l'un des premiers antirétroviraux de l'histoire du VIH. Le développement permanent de nouvelles molécules et l'amélioration de formes déjà existantes, afin d'améliorer le confort et la qualité de vie des patients, demeurent une préoccupation majeure des équipes de recherche. Ainsi Bristol-Myers Squibb a largement contribué à la simplification des traitements. C'est aujourd'hui le seul groupe pharmaceutique à proposer des molécules en une prise par jour dans les trois différentes classes d'antirétroviraux. Bristol-Myers Squibb vient également de lancer la première anti-protéase en une prise par jour.

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Pour des information sur le programme d'accès de Gilead Sciences, veuillez consulter le site Internet : www.GileadAccess.org.

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International Medical Press (IMP) publishes the peer-reviewed journals, Antiviral Therapy (ISI Impact Factor 6.57) and Antiviral Chemistry & Chemotherapy, and a range of books including Human Virus Guides series. IMP organises international conferences including the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (Washington, DC, 25-28 October 2004), and Therapies for Viral Hepatitis (Boston, MA, 2-3 November 2004). IMP also has a strong commitment to publishing through web-based communications.
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Our company is a pioneer in the development of drug resistance assays and has launched a performant innovative and rapid phenotypic assay called PHENOSCRIPT® to predict resistance to antiretroviral drugs used in HIV therapy.

PHENOSCRIPT® is available for clinicians and patients in the US and Canada thanks to Specialty Laboratories (www.specialtylabs.com) and in Europe, Middle East, Africa and Oceania thanks to Pasteur Cerba Laboratory (www.pasteur-cerba.com).

VIRalliance sets up collaborations directly with the pharmaceutical industry and academic organisations, virologists and clinicians to propose PHENOSCRIPT® for the development of new antiretroviral drugs and the evaluation of drug susceptibility during clinical trials.

VIRalliance commits itself to maintain PHENOSCRIPT® at the highest technological level and to understand antiretroviral resistance mechanisms including replicative capacity.

VIRalliance offre des services et technologies à fortes valeurs ajoutées pour optimiser le traitement des patients vivants avec le VIH.

Notre entreprise est un pionnier du développement de tests de résistance et propose un test de résistance phénotypique performant, innovant et rapide appelé PHENOSCRIPT® pour prédire la résistance aux antirétroviraux utilisés pour le traitement de l'infection par le VIH.

PHENOSCRIPT® est disponible pour les cliniciens et patients aux Etats-Unis et Canada via Specialty Laboratories (www.specialtylabs.com) et en Europe, Moyen Orient, Afrique et Océanie via le Laboratoire Pasteur Cerba (www.pasteur-cerba.com).

VIRalliance établit des collaborations directement avec l'industrie pharmaceutique et des organisations académiques, virologues et cliniciens, pour proposer PHENOSCRIPT® pour le développement de nouvelles molécules antirétrovirales et pour l'évaluation de la susceptibilité anti-virale au cours d'essais cliniques.

VIRALLIANCE concentre ses efforts et son expertise au maintien de PHENOSCRIPT® au plus haut niveau technologique et à la compréhension des mécanismes de résistance aux antirétroviraux incluant la capacité répliquative.

Contact : Jean-Louis Faudon
jeanlouis.faudon@viralliance.com

VIRCO BVBA

Putting knowledge into practice

Pioneers in the science of HIV drug resistance, we provide the most reliable, cost-effective and actionable drug resistance analyses available today for HIV patient management.

VirtualPhenotype™ combines a phenotypic analysis with a genotype to provide a more complete picture of drug resistance.

Antivirogram® is the only phenotyping assay validated in a prospective clinical trial, and provides a direct in vitro measure of drug resistance.

Virco provides the tools to help select what's best for HIV patients.

Mise en Pratique du Savoir

Pionniers dans la science de la résistance aux traitements antiretroviraux, nous fournissons les analyses les plus sûres, les plus efficaces par rapport aux coûts, et les plus pratiques, pour la prise en charge thérapeutique des personnes infectées par le VIH.

VirtualPhenotype™ donne une analyse phénotypique en combinaison avec un rapport génotypique, afin de fournir une compréhension plus complète de la résistance.

Antivirogram® est le seul test phénotypique validé dans un essai clinique prospectif; il fournit une mesure directe in vitro de la résistance.

Virco fournit les outils essentiels pour aider à améliorer la prise en charge thérapeutique des personnes infectées par le VIH.

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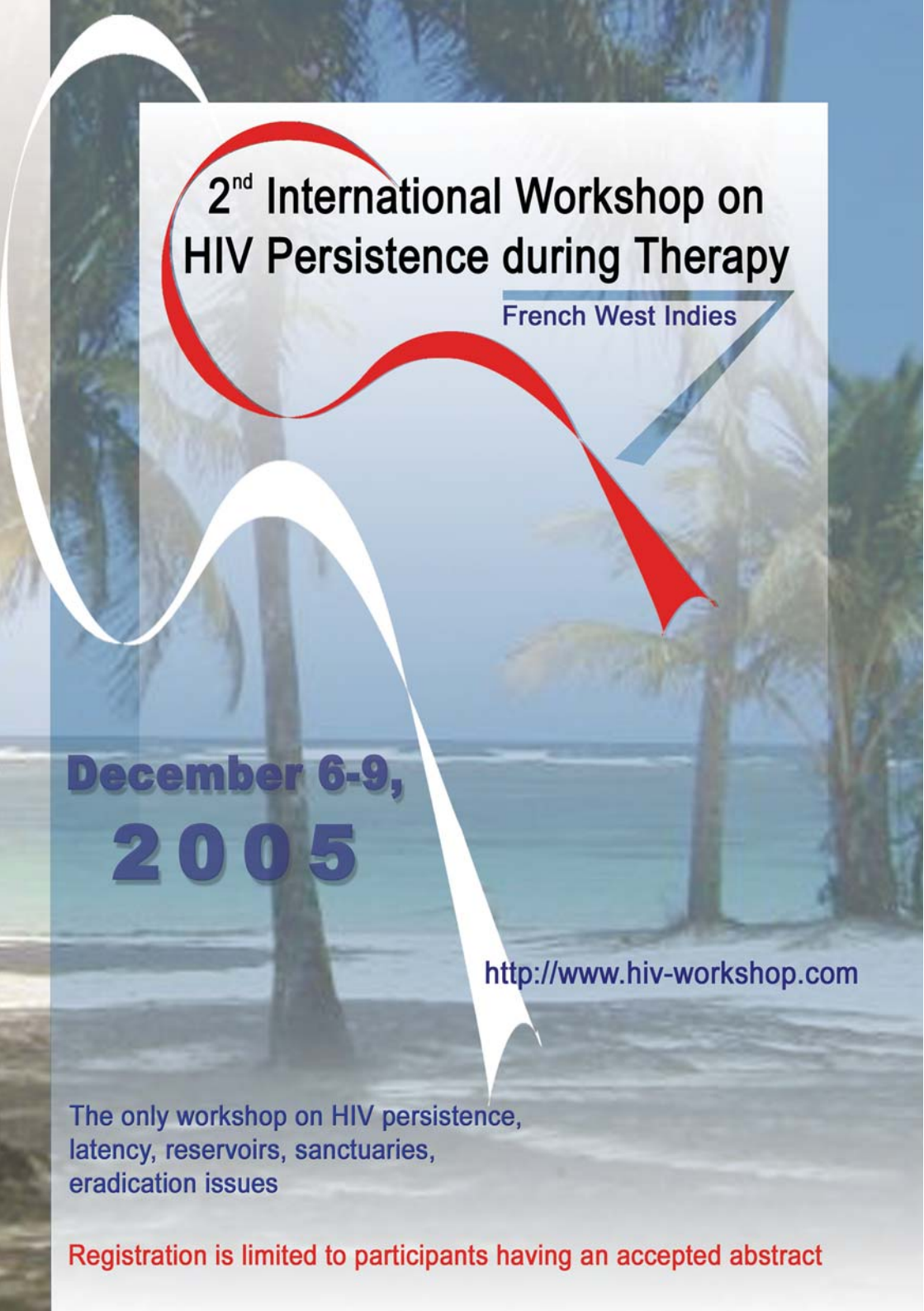
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